Investigating the developmental epidemiology of schizophrenia

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Investigating the Developmental Epidemiology of Schizophrenia

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Abstract of Thesis

The work presented in this thesis tracks developmental risk factors for schizophrenia from prenatal and perinatal life throughout childhood and into adult life in two epidemiological samples. This work provides new information on the nature and specificity of obstetric and childhood developmental risk factors for schizophrenia and schizophreniform disorder.

In structuring this thesis I first give a general introduction to the field of developmental epidemiology and the disease concept of schizophrenia. I then review the extensive literature on prenatal and perinatal risk factors for schizophrenia in Chapter 2. Chapter 3 provides a review of childhood developmental risk factors for schizophrenia concentrating on the evidence from genetic high-risk studies and general population birth cohort studies.

The original work that forms the basis of this thesis is outlined in Chapters 4 and 5. This work is derived from two population-based samples: a large nested case-control study from Helsinki, Finland and a general population birth cohort from Dunedin, New Zealand. This thesis finds childhood developmental risk factors for schizophrenia and schizophreniform disorder in both studies. In the Finnish study, poor performance in non-academic subjects and failure to progress to high school were risk factors for schizophrenia. In the Dunedin study, emotional, behavioural and interpersonal difficulties occurred in relation to a range of psychiatric disorders in adulthood, but early childhood impairments in motor, language and cognitive development were only found in association with schizophreniform disorder. There was evidence of a dose-reponse relationship between developmental impairment and risk of later schizophreniform disorder. Obstetric risk factors for later schizophrenia-spectrum disorders were noted in both studies. Low birth weight and low ponderal index were related to risk of later schizophrenia in an inverse linear fashion in the Finnish study. Hypoxia-related variables and small-for gestational age status were significantly related to schizophreniform disorder in the Dunedin Study. Controlling for the possible confounding effect of obstetric complications did not affect the strength of the relationship between developmental impairment and later schizophrenia outcome. In concluding the thesis I provide a synthesis of the findings from both studies.

Table of Contents

List of Tables and Figures

For David, Isabel and Dónal

"Would you tell me, please, which way I ought to go from here?"

"That depends a good deal on where you want to get to," said the Cat.

"I don't much care where .." , said Alice.

" Then it doesn't much matter which way you go," said the Cat.

"....so long as I get somewhere," Alice added as an explanation.

"Oh, you're sure to do that," said the Cat, "if you only walk long enough."

(Lewis Carroll, *Alice's Adventures in Wonderland*)

Chapter 1

Introduction and Aims

1.1 What is Developmental Epidemiology?

Definition

Epidemiology is the study of the distribution and determinants of disease frequency in human populations (Hennekens and Buring, 1987). The primary aims of epidemiological research are to explore issues dealing with the occurrence and distribution of diseases within a given population and the risk and/or protective factors that influence the distribution of the outcome of interest.

Epidemiological methods have been applied to the study of developmental outcomes that have their origins in the perinatal period, infancy, and childhood. The term developmental epidemiology was first coined in the 1970's (Kellam et al, 1983) and was originally confined to the study of the distribution of and risks for childhood disorders (Scott et al, 1994; Costello and Angold, 1995). However the term has now extended to include the study of early antecedents and risk factors for adult-onset and chronic diseases as well as childhood conditions, (Buka and Lipsitt, 1984). An alternative, commonly-used term is 'life course epidemiology', but this has a slightly narrower focus in that it confines itself to the study of chronic diseases of adulthood (Kuh and Ben-Schlomo, 1997).

Developmental psychopathology

Where the study of psychiatric illness is concerned there is a great deal of overlap between the fields of developmental epidemiology and developmental psychopathology (Cicchetti, 1984; Rutter, 1988). Developmental psychopathology has been defined as '*the study of the origins and course of individual patterns of behavioural maladaptation, whatever the age of onset, whatever the causes, whatever the transformations in behavioural manifestation, and however complex the course of the developmental pattern may be*' (Sroufe and Rutter, 1984) The key elements of developmental psychopathology are that the study of normal development informs the study of

psychopathological conditions (and vice versa) and, rather than development being predetermined or 'canalised', individuals are viewed as developing along flexible trajectories which can be influenced at any point in the lifespan to either increase or reduce the risk of disorder (Hollis and Taylor, 1997). According to this perspective, psychopathological disorders are not seen to emerge from the inevitable unfolding of a disease process but to arise out of a dynamic, transactional relationship between the development of the individual and the changing demands of the environment. The path between risk and outcome is not invariant. Thus the same risk factor may have multiple possible outcomes: this principle is known as multifinality, and equally, multiple pathways can lead to the same outcome, this principle is known as equifinality (Cicchetti, 1990).

Although epidemiological data have been used to tackle the questions posed in developmental psychopathology, the research issues are often formulated in ways that depart in some respects from traditional epidemiologic methods (Rutter, 1988). The common features of developmental epidemiology and developmental psychopathology include an interest in the process of disorder causation in the context of development, causal chain mechanisms and person-environment interaction. A developmental perspective posits a continuum between normality and abnormality, and evolution from static to more dynamic aetiologic theories of disorder. Although major advances have been made in both disciplines, much work remains to be done particularly in generating analytic and design methods that assess the impact of multiple causes and reflect multiple pathways to a common disorder, and in developing improved measurement techniques. The relatively new discipline of developmental epidemiology will lead to an enrichment of the design and analytic methods used in the study of psychopathology (Buka and Lipsitt, 1994).

Study design strategies in developmental epidemiology

To address the question of causation, two main analytic study designs are used in epidemiology: cohort studies which proceed from cause to effect, and case-control studies which look from effect to cause.

Cohort studies

Cohort studies can be either prospective or retrospective. A *prospective cohort study* is one in which researchers define an exposure that may be associated with a given outcome and then select exposed and unexposed subjects before the outcome of interest has occurred. The subjects are observed for a defined period of time during which all newly occurring cases of the outcome are identified. The prospective cohort study design is a powerful tool. It permits direct

measurement of the incidence of a given condition within a population. The time sequence is clear and strengthens the inference than the specific risk factor may be a cause of the outcome. A further advantage is that multiple outcomes of interest can be examined within a single study.

However in relating this study design to the study of childhood risk factors for adult illness, two main problems emerge. Firstly, if the outcome of interest does not occur frequently in the population, (eg schizophrenia), the cohort study must include very large numbers of subjects in order to accrue a meaningful number of cases. For instance schizophrenia occurs at a rate of 2-4 cases per 10,000 population per year (Jablensky et al, 1992) with a lifetime risk of 1/100. Therefore to observe 50 cases with schizophrenia up to age 45, as many as 5,000 children may be necessary for the study. Prospective studies become significantly more efficient as the outcome of interest becomes more prevalent (ie depression). The second important disadvantage relates to the fact that prospective cohort study designs often require a great deal of time for follow-up and data collection. If there is a long latency period between exposure and outcome, (as is the case with schizophrenia) the study will require sufficient resources for a follow-up period lasting many years, even decades.

Two strategies have been used to circumvent these problems and allow the use of the prospective cohort design for investigating the developmental epidemiology of schizophrenia. These strategies and the resulting findings are discussed in detail in Chapter 3. One strategy is to use enriched cohorts such as genetic high risk cohorts where the yield of cases of schizophrenia will be considerably higher (10-15% compared with 1%). The second strategy is to use existing birth cohorts that have already 'matured' or at least 'semi-matured'. The latter strategy has been used in this thesis (Chapter 5) in the analysis based on the Dunedin birth cohort. Considerably less time and expense are involved as the long latency period has already occurred. The design therefore becomes a type of *retrospective cohort study* as both the exposure and the outcome have occurred before the study has begun, and investigators 'scavenge' the cohort for childhood risk factors that may be of interest from a developmental viewpoint. It shares the advantages of a prospective cohort study in that there are clear temporal association between exposure and outcome and an ability to measure incidence and relative risk. However, because of the reliance on existing, historical information, researchers have minimal control over the quality and nature of the data collected. Data may have been measured and recorded in ways that are not optimal for answering the current research questions or certain information may not have been recorded at all. For instance, the Dunedin birth cohort is a very rich and detailed source of information regarding childhood development, but data on family history of schizophrenia or other psychiatric disorders are not available.

Case-control studies

Case-control studies choose subjects based on outcome status and look retrospectively from effect to cause. Study subjects are identified and grouped on the outcome of interest (cases and controls) and retrospective exposure and demographic data are used to identify possible risk factors. Cases and controls are compared with respect to the ratios of those having a history of an exposure or risk factor. Several advantages of the case-control study design make it a very useful research tool. A major strength is its efficiency in terms of cost and length of the study compared to the cohort design. Case-control studies can effectively examine outcomes of interest with a very long latency period of expression (such as schizophrenia). A second major strength of the case-control design is that it is efficient compared to other designs in the examination of rare or low prevalence outcomes. A final strength is that such a design allows for the examination of multiple potential risk factors.

The case-control methodology is not without weaknesses: the temporal link is not as clearly established as in a cohort design and only one outcome can usually be evaluated. However, the biggest drawback to the case-control design, and a genuine threat to its validity, is the increased potential for bias. Bias in epidemiological studies is a systematic error in the design, conduct or analysis that distorts or masks the true association between risk factors and outcomes. While bias can occur in any study design, case-control studies are particularly vulnerable because (1) study subjects are often identified and recruited though some organisational system (ie hospital, school, clinic) that many also be linked to personal characteristics, including the risk factors of interest (selection bias) and (2) investigators are often dependent upon the study subjects to self-report past exposures (information bias). A type of information bias that is of particular concern is recall bias – a situation in which the cases are more likely to report exposures that have occurred ot overestimate their exposure levels relative to the self-report of the control subject. The effect of such differential reporting would be to overestimate the association between the exposure and the outcome.

There are several steps that an investigator can take to prevent the occurrence of bias or minimise its effect within a case-control design and these strategies are illustrated in the Finnish study presented in Chapter 4 that forms part of this thesis. Selection bias can be prevented or reduced by using cases and control groups sampled directly from the defined populations of 'all cases' and 'all controls'. These population-based case-control studies are not affected by the eligibility criteria that may be associated with clinics or service agencies. The Finnish study in this thesis is an example of a *'nested case-control study'* (Rothman and Greenland, 1998; Langholtz and Thomas, 1990) where all cases are chosen from the defined population (ten year birth cohort in

one city) and one control per case was randomly chosen from the same population base. In this way a sample of over 400 cases of schizophrenia, diagnosed according to accepted diagnostic criteria, was available for the study compared with the much smaller numbers of cases usually available from cohort studies (usually less than one tenth that amount), with resulting high statistical power. A powerful strategy to reduce information bias is to use extant sources of information collected before the outcome of interest. The Finnish study (Chapter 4) makes use of standardised school records from 2-3 decades earlier that had been archived in Helsinki city.

Record linkage

The Finnish study in this thesis made use of record linkage to identify the case group. Three sources of information from health care registers were linked using a unique identifying number issued to all Finnish citizens in order to give information on diagnosis of schizophrenia in adulthood. Further linkage to the population register provided information on family history of schizophrenia. As a method of study, record linkage has early beginnings. Dunn, (1946) suggested the use of this method as a means of joining two independent data sets, recorded at different times or places, with information about the same individuals or families. Record linkage methodology has a number of advantages when applied to developmental epidemiology. It is useful in studying diseases or outcomes that have a long latency period and for low-prevalence conditions. Researchers can select an adequate sample size available from an extant database while incurring minimal time and financial burden.

Despite its advantages, it is important to note the limitations of record linkage methodology. The use of extant databases limits the information available, and the accuracy and completeness of the data entered are out of the control of the researcher. In addition, when linking two or more databases from different agencies, the data format may be discrepant and poses a challenge in assuring correct linkages, data analysis and interpretation. The computer hardware, software technology and computing expertise must be available to compete the data linkage correctly.

Analytic methods in developmental epidemiology

Major advances have been made in the study of large, complex datasets that include categorical variables, repeated waves of data collection, nested variables (ie children within families or schools), and missing data, all of which are likely to occur in developmental epidemiology. The data analytic methods used in developmental epidemiology draw on a variety of approaches recently described for the analysis of longitudinal observational data (Diggle et al, 1994).

The distinguishing feature of a longitudinal study is that the exposure and a set of covariates are measured repeatedly over time. Because repeated observations are made on the same individual, the repeated measurements on the exposure variable will usually be (positively) correlated. This within-subject correlation or autocorrelation must be accounted for into order to make correct inference. Therefore a model for longitudinal data has two components: a regression model for the dependence of the exposure variable on time and the covariates of interest; and a model for the autocorrelation among the repeated observations for an individual. In most cases the parameters of the regression model are of prime interest but estimates of these and their standard errors will be affected by the model chosen to describe the autocorrelation (Everitt, 1998). Fortunately, it is now relatively simple to build models for longitudinal data that allow consideration of a richer variety of correlational structures for the autocorrelation than older techniques such as ANOVA or MANOVA (Diggle et al, 1994; Everitt, 1999). The generalised estimating equation method (Liang and Zeger, 1986) has been introduced for the analysis of longitudinal, non-normal data where data consist of clusters of intercorrelated observations. In this approach, any required covariance structure and any link structure may be assumed, robust estimates of standard errors are provided and quasi-likelihood is generalised to take account of covariances of responses within clusters. A generalised estimating equation approach is used to analyse the repeated childhood developmental data in the Dunedin study described in Chapter 5.

Sometimes the amount of variability within individuals is the main focus of the analysis, for instance in the analysis of cognitive development. Mixed and multilevel models including growth curve models can be used for such analyses (Goldstein, 1995; Taylor et al, 1998). Methods for the analysis of growth have become more easily accessible with the development of software for multilevel models such as MLwiN (Goldstein et al, 1998), and other programs for random effects modelling such as STATA (StatCorp, 1995, 1999; Rabe-Hesketh and Everitt, 2000). These programs require neither the number of observations nor the intervals of time between observations to be the same for all subjects, making them applicable to a much wider range of clinical and epidemiological studies than their less flexible predecessors (Taylor et al, 1998).

Another issue for the analysis of longitudinal data is the issue of data hierarchies (Goldstein, 1995). Many kinds of data have a nested or clustered structure. For example, children are nested within families and will tend to be more alike than children from different families. Students are nested within classes or schools, and individuals and families are nested within neighbourhoods. Repeated measures data can also be viewed as data clustered within one individual. A hierarchy consists of units grouped at different levels. Thus students may be the level 1 units clustered within schools - the level 2 units. Multilevel analysis will allow the optimal examination of this

type of hierarchical data. Software packages such as MLwiN (Goldstein et al, 1998) have been developed for this purpose. In this thesis, multilevel analysis is used to examine the data on school records in the Finnish study (Chapter 4). The data is viewed as a 3-level structure: repeated grades nested within individuals who are nested within schools.

Missing data is an important consideration in the analysis of longitudinal data. The 'older' approach of complete case analysis uses only the subset of subjects with no missing values. The procedure is valid only when the values are missing completely at random (which is rarely the case), and even then is highly inefficient if a large proportion of subjects have to be discarded. If data are missing not completely at random then the results of the analysis will be seriously biased. One could replace the missing values with imputed values such as cross-sectional means or 'last observation carried forward', but this is not a satisfactory approach. Fortunately, the more recently developed techniques for analysing longitudinal data (Diggle et al, 1994) are specifically formulated so that they can accommodate non-informative missing values in the models used. Consequently such missing values raise no problems in the estimation of parameters or their standard errors.

Risk factors and causes

Although a primary aim of epidemiology is to identify the causes of disease, most researchers prefer to use the term risk factors or risk markers rather than cause. As Costello and Angold (1995) point out, '*In practice causal investigations rarely yield the pure, unique, perfectly predictable connection between two phenomena that etiologic research aims for.*' The term 'risk factor' was coined by cardiovascular epidemiologists in the 1960s when longitudinal community studies showed that their initial hypothesis of a single cause for cardiovascular disease was not true. A risk factor is a measurable characteristic of each subject in a specified population that precedes the outcome of interest and which can be used to divide the population in some way into high-risk and low risk groups (Kraemer et al, 1997). The subject may be an individual person but it may also be a family, a class or a community. Crucial to the definition of a risk factor is the requirement that it precedes the outcome of interest. In practice, as discussed earlier, the safest course is to use a prospective longitudinal study design to determine risk factors. A statistically significant association between risk factor and outcome must be established. The potency of the risk factor is measured using a statistical summary measure such as odds ratio, relative risk, risk ratio, as well as methods for their point and confidence interval estimation.

Types of risk factors

A risk factor that can be demonstrated to change spontaneously within a subject (eg age or weight), or to be changed following an intervention (such as drugs or psychotherapy) can be called a *variable risk factor*. (Kraemer et al, 1997), a risk factor that cannot be changed is a *fixed marker* (eg race, sex, year of birth). If there is no empirical evidence documenting the stability or variability of a risk factor within subjects, the appropriate term is risk factor. A variable risk factor that can be shown to be manipulable, and when manipulated, can be shown to influence the risk of outcome we term a *causal risk factor*. The label that is appropriate depends on the current state of scientific knowledge about that factor. Developmental deficits can be thought of as fixed markers. However if an intervention can be shown to improve the deficits they then become variable markers. If this intervention ultimately affects outcome then the term causal factor can be applied. In the research literature on risk factor estimation, terms such as risk, marker, and cause are used in various ways. The same construct is often referred to by different terms. A fixed marker may also be termed a vulnerability factor or a susceptibility factor. In psychiatric epidemiology there is a great deal of research evidence for correlates and fixed markers but less evidence for variable risk factors (specifically from longitudinal population studies). The word 'cause' suggests a necessary and sufficient condition for the disorder, a single cause. This notion is often inappropriate as cause has multiple meanings based on recognition of the dependence of various causal influences on each other, the effect of multiple causes and the multiple paths leading to an outcome. For instance unprotected sex and shared needles are causal risk factors for AIDS but the cause of AIDS is the human immunodeficiency virus, in the absence of which unprotected sex and sharing of needles would have no influence.

The importance of defining risk factors is linked to the relevance of the factor for risk management. For instance if one had to choose a limited population to target for a prevention programme one would choose a population high on fixed markers. However in devising the preventive intervention, one needs to target causal risk factors. Generally fixed markers are easier to measure and recognise and are important in that they stimulate theories about possible causal mechanisms. However the complete understanding of the cause and course of any disease requires a focussed search for causal risk factors.

1.2 What is schizophrenia?

The evolution of the diagnostic concept of schizophrenia

Kraepelin (1856-1926)

The disease entity nowadays called schizophrenia was first delineated by Emil Kraepelin. In the fourth edition of his textbook in 1983, dementia praecox first appeared under the heading of 'Psychic Degenerative Processes' (Kraepelin, 1893). In later editions dementia praecox begins to appear as an entity of its own. Kraepelin used the term dementia praecox to stress the early onset of the illness and the permanent deterioration of mental functioning it causes among the great majority of patients. He defined dementia praecox as "*a series of states, the common characteristic of which is a peculiar destruction of the internal connections of the psychic personality. The effects of this injury predominate in the emotional and volitional spheres of mental life*" (Kraepelin, 1919). Kraepelin detailed the symptoms commonly occurring in schizophrenia: hallucinations, delusions, incoherence of thought and speech, catatonic symptoms, disordered attention, disordered judgement, emotional dullness, avolition and autism. However he considered no symptom pathognomic for the condition. He considered dementia praecox to be a developmental disorder characterised by an early onset, an organic basis and a deteriorating course. Nowhere is there any precise demarcation of the illness only an overall picture. Hoenig (1983) notes '*the methodologically unique state of affairs*', that Kraepelin had created the disease entity of dementia praecox without being able to name a single unequivocal symptom of it.

Bleuler (1857-1939)

In the introduction to his monograph, Bleuler (1911) stresses what his work has in common with that of Kraepelin. "*The whole idea of dementia praecox originates with Kraepelin; also the grouping and description of the individual symptoms we also owe entirely to him*", but proceeds to point out that "*The name (dementia praecox) can only be used to refer to the illness not the patient and it does not permit the formulation of an adjective which could characterise the properties of the illness*" (Bleuler, 1911). Hoenig (1983) dryly observes that "*One almost gets the impression that the only noticeable intention of the monograph was to replace the name dementia praecox by that of schizophrenia and that mostly for grammatical reasons.*" However apart from changing the name, Bleuler differed from Kraepelin in that he did not consider outcome important and placed more emphasis on phenomenology. Bleuler's diagnosis of schizophrenia was based on fundamental symptoms, relating to association, affectivity, attention, ambivalence and autism, though not all of them needed to be present in a given patient.

Although Bleuler had not intended to create a new diagnostic concept, his term 'schizophrenia' displaced 'dementia praecox', and gradually the concept of schizophrenia became broadened to include non-specific symptoms that lay on the borderline of normality, eccentricity and personality variants (Hoenig, 1983). Various names for these marginal cases were invented such as 'latent schizophrenia', 'schizoid psychosis', 'schizophreniform'. In 1933, the German Reich passed a law that stipulated compulsory sterilisation of all cases of schizophrenia and other hereditary mental illnesses and this considerably reduced the use of the term schizophrenia in Germany. However, in the United States the broad Bleulerian approach which heavily emphasised thought disorder remained dominant and influenced the American Psychiatric Association (APA) when drawing up the first two editions of the Diagnostic and Statistical Manual of Mental Disorders (DSM, DSM-II), (APA, 1952, 1968).

Diagnostic and Statistical Manual of Mental Disorders (DSM)

Several factors led to a reconceptualization of schizophrenia in DSM-III (APA, 1980). During the 1960's and the 1970's it became evident that American psychiatrists were diagnosing schizophrenia much more commonly than their British (and Nordic) counterparts who had remained true to the Kraepelinian approach (Cooper et al, 1972). The large variation in diagnostic practices promoted the development of scientific nosology in psychiatry, (Kendler, 1990). The Washington University or St Louis or Feighner criteria published in 1972 represented the first diagnostic classification validated primarily by follow-up and family studies rather than by clinical judgement and experience (Feighner et al, 1972) and were strongly influenced by Kraepelin's views of schizophrenia. The DSM-III (APA, 1980) drew heavily on both the Feighner criteria (Feighner et al, 1972) and the Research Diagnostic Criteria (Spitzer et al, 1978) in its reformulation and narrowing of the concept of schizophrenia. Schizophrenia was defined as a chronic disorder lasting at least 6 months, characterized by deteriorated vocational and interpersonal functioning (APA, 1980). Superimposed on this enduring state were one or more active phases or episodes characterised by the presence of acute psychotic symptoms. One difficulty inherent in the DSM-III concept of schizophrenia was that, if it emerged relatively early in the life span, deterioration of functioning was less apparent because of the individual's failure to develop normally. The DSM-III-R (APA, 1987) essentially simplified the DSM-III rules for diagnosing schizophrenia and broadened the developmental considerations by requiring that an individual show evidence of either a decline in functioning or a failure to achieve expected levels of achievement. A time duration of one week was set for the acute phase symptoms. The fourth (current) edition of the DSM (APA, 1994) is very similar to DSM-III-R in that it maintains a similar developmental emphasis (Table 1.1). However the time duration for active symptoms has been extended to one month and hallucinations are no longer required to be

prominent. DSM-IV uses the term 'disorganised speech' instead of ' incoherence or marked loosening of associations' for schizophrenic thought disorder. Grossly disorganised behaviour is included as a symptom criterion. Negative symptoms are included for the first time in the DSM system.

Table 1.1 DSM IV Diagnostic Criteria for Schizophrenia (APA, 1994)

A. Characteristic symptoms: Two or more of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated): 1. Delusions 2. Hallucinations 3. Disorganised speech 4. Grossly disorganised or catatonic behaviour 5. Negative symptoms Only one Criterion A symptom is required if delusions are bizarre or hallucinations consist of a voice keeping up a running commentary on the person's behaviour or thoughts, or two or more voices are conversing with each other.
B. Social/occupational dysfunction: for a significant portion of the time since the onset of the disturbance, one or more major areas of major functioning such as work, interpersonal relations or self care are markedly below the level achieved prior to the onset (or when the onset is in childhood or adolesence, failure to achieve the expected level)
C. Duration: Continuous signs of the disturbance persist for at least 6 months, of which at least one month should be of symptoms that meet Criterion A. The six months may include periods of prodromal and residual symptoms.
D. Schizoaffective and mood disorder exclusion: Schizoaffective disorder and mood disorder with psychotic features have been ruled out because either no major depressive, manic or mixed episodes have occurred concurrently with the active phase symptoms, their total duration has been brief relative to the active and residual periods.
E. Substance/general medical condition exclusion: The disturbance is not due to the direct physiological effects of a substance or a general medical condition.
F. Relationship to a pervasive developmental disorder: If there is a history of autistic disorder or another pervasive developmental disorder, the additional diagnosis if schizophrenia is made only if prominent delusions or hallucinations are present for at least a month (or less if successfully treated).

Schizophreniform disorder

The term 'schizophreniform psychosis' was first coined by Gabriel Langfelt in 1937 (Langfelt, 1937). As originally used, this diagnosis relied on a tradition of Scandinavian psychiatry, which had identified a condition that had relatively few, self-contained psychotic intervals. Patients recovered and had affective and sometimes hysterical components to their illness. The diagnosis was used to distinguish a group considered to have little relation to true schizophrenia.

In contrast, the current DSM-IV diagnosis of schizophreniform disorder has relatively little to do with the origin of the term and much to do with the tradition of Kraepelinian schizophrenia as an illness (Table 1.2). Prior to the DSM-IV revision of this diagnostic entity, DSM-III and DSM-III-R had used this diagnosis as a type of 'schizophrenia-in-waiting' with the only difference between the two diagnoses being whether the illness had lasted a total of 6 months. Under the DSM-III and DSM-III-R system, the psychotic phase of the illness needed to last only one week. The remainder of the 6-month duration criteria for schizophrenia comprised residual or prodromal symptoms. Patients who had an insidious onset with prodromal symptoms preceding the onset of psychotic symptoms by at least 6 months would be given a diagnosis of schizophrenia as soon as the psychotic symptoms had lasted one week. Those who had limited prodromal symptoms or who had a sudden onset of psychosis would not be diagnosed until the total period of the illness lasted 6 months. In the meantime the diagnosis of schizophreniform disorder would be used. Therefore the category of schizophreniform disorder formerly consisted of patients with potentially many types of psychosis: brief reactive psychosis, 'schizophrenia-in-waiting' and true schizophreniform disorder. True schizophreniform disorder is probably quite rare compared to the other categories although important as a time-limited psychotic illness that returns to baseline functioning without residual symptoms. Data from the Epidemiological Catchment Area survey indicated a lifetime prevalence of 0.2 percent and a 1-year prevalence of 0.1 percent for DSM-III schizophreniform disorder (Robins and Regier, 1990).

The revisions of DSM-IV have made the overlap with brief reactive psychosis less likely. The DSM-IV diagnosis for schizophreniform disorder (Table 1.2) requires one month of psychotic symptoms rather than one week and the diagnosis has moved much closer to its parent diagnosis of schizophrenia. The requirement for a greater duration of psychotic symptoms makes it less likely that a given patient will recover before 6 months of total illness. The category now looks like schizophrenia with an unanticipated full recovery before 6 months. Whether this represents a separate disorder category or merely one end of the schizophrenia spectrum is yet to be

determined. There are currently no published epidemiological data from community surveys on the prevalence of DSM-IV schizophreniform disorder. At present social or occupational dysfunction is not required to meet the diagnosis. However given the requirement of one month of psychotic symptoms, it seems likely that a person's social and occupational functioning would be disrupted. Schizophreniform disorder (DSM-IV) is the main psychiatric outcome examined in the analysis of the Dunedin birth cohort presented in Chapter 5.

Table 1.2 DSM-IV diagnostic criteria for Schizophreniform Disorder (APA, 1994)

A. Criteria A, D, and E of Schizophrenia are met
B. An episode of the disorder (including prodromal, active and residual phases) lasts at least 1 month but less than 6 months. (When the diagnosis must be made without waiting for recovery, it should be qualified as 'Provisional')
Specify if: **Without Good Prognostic Factors** **With Good Prognostic Features**: as evidenced by two (or more) of the following): (1) onset of prominent psychotic symptoms within 4 weeks of the first noticeable change in usual behaviour or functioning (2) confusion or perplexity at the height of the psychotic episode (3) good premorbid social and occupational functioning (4) absence of blunted or flat affect

International Classification of Diseases (ICD)

The International Classification of Diseases (ICD) is a disease classification system developed by the World Health Organisation (WHO) to promote international comparability of health care statistics. The eighth revision of the ICD, launched in 1967 (WHO, 1967), placed considerable emphasis on Schneiderian first rank symptoms in its description of schizophrenia. It included seven subtypes of schizophrenia. The simple type was characterized by oddities of conduct, difficulties in social relationships and decline in overall performance, but without clear-cut symptoms of schizophrenia. Typical symptoms of the hebephrenic type were inappropriate affect, bizarre or catatonic behaviour, and prominent thought disorder. The catatonic type was characterized by catatonic symptoms, and the paranoid type by prominent delusions and

hallucinations. In the acute schizophrenic episode, the onset of schizophrenic symptoms was acute and a dream-like state with slight clouding of consciousness and perplexity were often present. The latent type was characterized by the emergence of symptoms not obviously schizophrenic but severe enough to raise a strong suspicion of schizophrenia. The residual type was reserved for chronic residual states in which fragments of faded schizophrenic symptomatology occurred. In addition, 'other' and 'unspecified' types were reserved for patients who did not fit into other subtypes. Infantile autism was regarded as part of schizophrenia.

In the ninth edition of the ICD, published in 1977 (WHO, 1977), the description of schizophrenia had hardly changed from ICD-8. However, childhood type schizophrenia and infantile autism were removed and the use of simple and latent schizophrenia were discouraged.

The tenth edition of the ICD was published in 1992. It is the first ICD edition to provide operationalized diagnostic criteria for research purposes. The required duration of symptoms is considerably shorter than in DSM-IV (one versus six months) and ICD-10 does not require deterioration from a premorbid level of functioning. ICD-10 included negative symptoms and the mood disorder exclusion criterion requires that the onset of psychotic symptoms must have preceded the onset of mood symptoms.

The Finnish study described in Chapter 4 uses ICD 8 and ICD 9 diagnostic criteria for schizophrenia. However there are some particular aspects of the application of ICD diagnostic systems in Finland that are outlined below.

Diagnostic criteria for schizophrenia in Finland

Between 1969 and 1986, the official diagnostic classification used in Finland was ICD-8. However the diagnostic concept of schizophrenia applied by Finnish clinicians was very narrow. In a study of first contact patients with schizophrenia or schizophreniform disorder in Helsinki in 1975, only 52% of the patients who received a DSM-III diagnosis of schizophrenia had received a hospital discharge diagnosis of schizophrenia or schizophreniform disorder (Kuusi, 1986). In another study of all first admissions to Helsinki's two psychiatric hospitals in 1981, 35% of the patients received a diagnosis of schizophrenia (S+) or borderline psychosis (O+) as assigned by the CATEGO computer program based on the Present State Examination interview conducted blind to clinical diagnoses, but only 19% had received a clinical diagnosis of schizophrenia or schizophreniform disorder (Pakaslahti, 1987). An incidence study carried out between March 1 1983 and February 29 1984 covering six health care districts in Finland, (Salokangas, 1993)

found that clinicians made a DSM-III diagnosis of schizophrenia less often than an independent researcher.

In 1987 the general medical diagnostic classification system in Finland was updated to ICD-9. However the diagnostic criteria for mental disorders were adapted with slight modifications from DSM-III-R. In this system, the first four numbers in the diagnostic codes corresponded to the ICD-9 code, but the fifth digit was unique to the Finnish coding system and allowed for subclassification similar to that used in DSM-III-R. The diagnostic criteria for schizophrenic psychoses were identical to the DSM-III-R criteria, but unlike in DSM-III-R schizophreniform and schizoaffective psychoses were classified as schizophrenic psychoses (Kuoppasalmi et al, 1989). Studies comparing research and clinical DSM-III-R diagnoses conducted in the 1990s found a continuing tendency for Finnish researchers for apply a narrow definition of schizophrenia. Isohanni et al (1997) compared clinical (hospital register) and research diagnoses of schizophrenia in the North Finland 1966 birth cohort. He found 71 patients fulfilling DSM-III-R criteria for schizophrenia but only 37 of them had a hospital discharge register diagnosis of schizophrenia. In a sample of patients from one municipality, 87% with a schizophrenia diagnosis and 18% with a schizophrenia spectrum diagnosis in the register fulfilled DSM-III-R criteria for schizophrenia (Mäkikyrö et al, 1998). The Finnish study described in Chapter 4 used ICD 8 and 9 diagnoses of schizophrenia. Since 1996, ICD-10 diagnostic codes and criteria have been used in Finland.

1.3 Aim of this thesis and statement of authorship

The aim of this thesis is to investigate prenatal, perinatal and childhood developmental risk factors for schizophrenia in adulthood using the methods of developmental epidemiology. Two large population-based studies are analysed for this purpose: a nested case-control study in Helsinki, Finland and a general population birth cohort in Dunedin, New Zealand.

I designed and carried out the statistical analysis on all studies reported in this thesis. In addition I carried out the data collection for the school record study in Helsinki, Finland and I co-ordinated and assisted with the data collection for the birth record study in Helsinki, Finland. All work was carried out while I was supported by the Wellcome Trust.

Chapter 2

Background: Pre-and perinatal risk factors for schizophrenia

2.1 A neurodevelopmental model of schizophrenia

Central to the search for prenatal and perinatal risk factors for schizophrenia as outlined in this chapter is the notion of schizophrenia as a neurodevelopmental disorder. The so-called 'neurodevelopmental hypothesis' of schizophrenia proposes a subtle deviance in early brain development whose full adverse consequences are not manifest until adolescence or early adulthood. It came to prominence in the late 1980's (Murray & Lewis, 1987, Weinberger, 1987) though similar models had been proposed by other researchers decades, even centuries, earlier (Clouston, 1891, 1892, Southard, 1915).

The 1980s version of the 'neurodevelopmental hypothesis' originated from a number of strands of evidence available at that time, including retrospective studies revealing a pattern of abnormalities in neurological and behavioural parameters dating back to childhood (Watt, 1978, Aylward et al, 1984), histopathological studies indicating that developmental processes may have gone awry in the formation of the hippocampus (Kovelman and Scheibel, 1984, Jacob and Beckman, 1986), and neuroimaging studies showing cerebral ventricular enlargement, (Johnstone et al, 1976, Weinberger et al, 1979), even at the time of the first episode (Turner et al, 1986). Not all of this evidence has withstood the test of time and replication, particularly the original histopathological findings. However, new information has emerged to provide support and further clarification of the neurodevelopmental hypothesis, including epidemiological investigations, longitudinal studies of high-risk offspring, advances in magnetic resonance imaging and more recent neuropathological investigations (for review see Marenco and Weinberger, 2000, McDonald and Murray, 2000).

In fact, the neurodevelopmental hypothesis is not really a hypothesis at all, rather an aetiological model that directs research towards early life (Jones, 1999a). These early risk factors for schizophrenia represent some of the most challenging and interesting targets of schizophrenia epidemiology.

2.2 Prenatal risk factors for schizophrenia

2.2.1 Time and place of birth

Winter birth

An association between severe psychiatric disorder and season of birth was noted by Tramer (1929). More than 250 studies, covering 29 Northern and five Southern Hemisphere countries, have been published on the birth seasonality of individuals who develop schizophrenia and/or bipolar disorder. Despite methodological problems, the studies are remarkably consistent in showing a 5-8% winter-spring excess of births for both schizophrenia and mania/bipolar disorder. (Hare et al, 1974; Bradbury & Miller, 1985). Detailed reviews of this literature are provided by Cotter et al (1996), and Torrey et al. (1997).

This 'season of birth effect' has caused debate for decades (e.g Lewis & Griffin, 1981; Lewis, 1989; Watson et al, 1982; Torrey & Bowler, 1990a; Torrey et al., 1993) and has had a large impact on the developmental epidemiology of schizophrenia. It appears to be a robust finding, at least in the Northern Hemisphere (Hare, 1975; Kendell & Adams 1991; Mortensen et al, 1999), although the effect seems to be absent, or at least much weaker, in the Southern Hemisphere (McGrath and Welham, 1999). Regarding the cause of the birth seasonality, differential fertility and breeding patterns are unlikely explanations (Hare, 1976). An environmental factor that fluctuates with the season and has its effects around the time of birth is the presumptive explanation and seasonal infections are the most popular candidate (Torrey et al, 1997).

Urban birth

The risk of developing schizophrenia has been found to be increased among those born in cities compared with those born in rural areas (Torrey et al, 1990b, Lewis et al, 1992, Takei et al, 1995a, Marcelis et al, 1998, Mortensen et al, 1999), though, again, effect sizes are small, ranging between 1.5 to 2.5. Linear trends for risk of schizophrenia with increasing population density of area of birth have been noted (Marcelis et al 1998, Mortensen et al, 1999). However one must bear in mind that urbanicity is a variable that is defined in 'relative' terms ie Copenhagen in relation to the rest of Denmark. The effect of 'urbanicity' is likely to be rather different in Beijing or Bombay compared with Copenhagen. Many earlier studies presented good evidence that the excess of schizophrenia found in the central areas of large cities was largely due to migration into these areas of adolescents and young adults a few months or years before they developed overt schizophrenia,

(Gerard and Houston, 1953; Hare, 1956). Therefore attempts have been made to tease apart the effects of urban birth and urban living (in adulthood). Marcelis et al (1999) found that the greatest risk was for those born in urban areas with no additional effect of later urban residence. Urban dwellers who were not born in the city were not at increased risk of schizophrenia. These results indicate that the urban risk factor or factors associated with an increase in risk of schizophrenia appear to act in early life rather than around the time of illness onset.

Immigration

Interest in the association between immigration and schizophrenia was fuelled by a report by Harrison and colleagues that the first-contact incidence rate for schizophrenia among the African-Caribbean population in Nottingham was 10 times higher than the rate in the general population (Harrison et al, 1988). This finding has been convincingly replicated in other centres in the UK (Wessley et al, 1991; Thomas et al, 1993, King et al, 1994; Van Os et al, 1995), and in the Netherlands (Selten et al, 1994), although the incidence ratio is now thought to be nearer 2 or 3 when the denominator is adjusted for possible under-reporting in the census data. An increased incidence ratio for schizophrenia has also been found among other immigrant groups in the UK also, indicating that the effect is not confined solely to the African-Caribbean immigrants (King et al, 1994).

There are some interesting features of the association between migration and schizophrenia that may help to elucidate causality:

1) Second generation migrants are at much greater risk than first generation migrants arguing against the 'selective migration' hypothesis (ie the explanation that individuals with premorbid features of schizophrenia are more likely to migrate). (2) There is evidence that immigrants from poor countries to rich countries show higher rates of schizophrenia than immigrant groups from more affluent countries (Warner, 1995), implying that some factor associated with improvement in living conditions, industrialisation or urbanisation may increase the risk of schizophrenia among migrants. Possible explanations are: a change in diet during pregnancy, increased rates of obstetric complications among immigrant mothers, the increased survival of low-birthweight immigrant infants, or exposure to new viruses during pregnancy (Eagles et al, 1991). (3) Several studies indicate that the hospital admission rates for schizophrenia among migrants are higher than in their country of origin,(Odegaard, 1932; Burke, 1974; Hickling, 1991) suggesting that the higher rate among migrants is due to some factor operating principally within the host country and arguing against the theory that cannabis use is responsible for the increased rates of schizophrenia among the Afro-Caribbean immigrants. A greatly-increased risk of schizophrenia has been found in the siblings of UK-born Afro-Caribbean patients with schizophrenia

(Sugarman et al, 1994, Hutchinson et al, 1996) If replicated this could provide important evidence of gene-environment interaction ie an environmentally-mediated factor operating upon genetically predisposed individuals.

However no studies have controlled adequately for all possible confounders such as low socioeconomic class and marital status which may reduce the incidence ratio even further. It is likely that ethnicity and immigration, like urban birth and winter birth, represent 'proxy' variables for various biological and perhaps social risk factors. Once these are controlled there may be little or no effect of place or time of birth in themselves but we would gain information about other, perhaps preventable risk factors for schizophrenia.

2.2.2 Prenatal infection as a risk factor for schizophrenia

Prenatal influenza

Much of the evidence regarding the role of prenatal infections has come from ecological, or population-association studies. The most influential of these were inspired by Mednick and colleagues (1988) who demonstrated that women who were in the second trimester of pregnancy during the 1957/58 influenza A_2 pandemic in Helsinki were about twice as likely to be hospitalised with a diagnosis of schizophrenia as those not exposed during pregnancy or exposed earlier or later in pregnancy. There have been many attempts at replication of this exciting finding regarding the 1957 epidemic in different populations using an ecological design, (O'Callaghan et al. 1991; Kendell & Kemp, 1989; Mednick et al., 1990; Kendell & Adams, 1991; Torrey et al, 1992; Erlenmeyer-Kimling et al., 1994; McGrath et al, 1994, Kunugi et al, 1995, Izumoto et al, 1999). The effect sizes demonstrated in these studies are small - somewhere between 1.5 and 2.0 (Cannon and Jones, 1996); and not all ecological studies have replicated the association (Kendell and Kemp, 1989; Torrey et al, 1988; Selten and Slaets, 1994; Susser E et al, 1994), but this is not inconsistent with a small effect on the threshold of detectability. The balance of evidence suggests that maternal influenza in this epidemic was associated with a raised incidence of schizophrenia if it occurred in the second trimester of pregnancy, particularly the 5^{th} or 6^{th} month, (see McGrath et al, 1995, Wright et al, 1999 for review). In most studies where the sexes are examined separately, the positive association was found mainly or exclusively in females, (Kendell and Kemp, 1989; Mednick et al, 1990; O'Callaghan et al, 1991, McGrath et al, 1994; Adams et al, 1993; Takei et al, 1994, 1996; Izumoto et al, 1999) but no satisfactory explanation has yet been offered for this. Likewise, the association with prenatal influenza does not adequately account for the 'season-of-birth effect' reviewed in the previous section (Torrey et al, 1991).

Studies of longer-term trends in the association between the timing of influenza epidemics and the birth dates of people with schizophrenia have yielded generally positive results in most (Barr et al, 1990, Sham et al, 1992, Adams et al, 1993, Takei et al 1994), but not all cases (Torrey et al, 1988; Selten and Slaets, 1994; Morgan et al, 1997,). Studies based on whole countries or large regions (such as Western Australia), will, in general, be less powerful than those based solely in urban areas where infection is concentrated (Kendell and Kemp, 1989), and studies based on highly mobile populations such as the USA (Torrey et al, 1988) will be weak because the ecological design assumes that most people are still living in the state or region in which they were born when they develop schizophrenia two or three decades later.

Undoubtedly, the ecologic design has limitations. There may be unknown confounding with other factors, such as maternal fever or medication, that could explain the association. The so-called 'ecological fallacy' means that we cannot be certain that the individuals in the population who were exposed to influenza in utero are the same individuals who are diagnosed with schizophrenia as adults.

The next step therefore was the application of cohort and case-control methodology to this question. Two case-control studies have replicated the association between second trimester exposure to influenza and later schizophrenia, (Stöber et al, 1992; Wright et al, 1995) but confirmation of the exposure relied on maternal recall, which casts doubt on the validity of the findings. Two cohort studies have failed to support the influenza-schizophrenia association (Crow and Done, 1992; Cannon M et al, 1996). The British 1958 birth cohort study (National Child Development Study) collected information on all children born in one week in March 1958. After they had given birth in the original survey, mothers were asked whether they had suffered influenza (the 1957 A_2 pandemic) during pregnancy. There was no association between reported maternal influenza and schizophrenia in the offspring (Crow et al., 1991; Crow and Done, 1992). Cannon and colleagues (1996) followed a group in Dublin who had been exposed to the same 1957 pandemic. Valid information on exposure had been collected for an earlier report by Coffey & Jessop (1959; 1963). There was no evidence of an excess of schizophrenia in the exposed group during adult life, although a secondary analysis suggested a link with affective disorder. The negative results of these cohort studies must, of necessity, be viewed in the light of their limited power to detect an effect (Adams and Kendell, 1996), and the evidence that self report of influenza infection is not an accurate indication of serological infection (Elder et al, 1996). Certainly the prevalence of recall of pregnancy infection in the NCDS (Crow and Done, 1992) was much lower than would have been expected given the severity of the influenza pandemic only a few months previously.

Other prenatal infections

Interest in prenatal infection as a risk factor for schizophrenia is not restricted to influenza. Indeed, there is little reason to suppose that such an effect would be specific. Influenza happens to lend itself to study because of the frequent occurrence of well-defined epidemics. Brown et al (2000a) showed that second trimester exposure to a wide variety of respiratory infections (including influenza, pneumonia, tuberculosis and acute bronchitis among others), was associated with a significantly increased risk of schizophrenia spectrum disorders in the Prenatal Determinants of Schizophrenia Study (adjusted relative risk=2.13). These results indicate that several infections, both bacterial and viral, may increase the risk of schizophrenia through some common pathogenic mechanism. An ecological study from Finland by Suvisaari and colleagues (1999) found an association between second trimester exposure to poliovirus infection and later schizophrenia. Jones and colleagues (1999b) have followed a large group of individuals whose mothers were identified during pregnancy as suffering from identified viral infections (Fine et al, 1985) and have found evidence relating neurotropic virus exposure with a range of adverse CNS outcomes, including mental retardation, epilepsy and psychosis.

Prenatal rubella

Brown and colleagues (2000b) investigated a cohort of individuals who were serologically documented to have sustained in utero exposure to rubella and found that the rubella-exposed subjects, most of whom were exposed in the first trimester, had a substantially higher risk (relative risk =5.2) of developing nonaffective psychoses than those who were not exposed, independent of hearing status. The cohort design with proof of individual exposure status is robust, and the effect size for the association between prenatal rubella and schizophrenia is much larger than that reported for prenatal influenza. These findings suggest that nonaffective psychosis may be a remote, hitherto unrecognised neuropsychiatric consequence of prenatal rubella.

Neonatal and early childhood infection

The time window during which early exposure to infection may exert an effect appears to extend beyond birth and into childhood. The North Finland 1966 birth cohort contains all live births (12,058 in total), to women in northern Finland (Oulu and Lapland provinces) during 1966 (Rantakallio, 1969). Rantakallio and colleagues (1997) identified through record linkage all cohort members who had been hospitalised during childhood for a central nervous system (CNS) infection (mainly encephalitis and meningitis). They then identified those members of the cohort

who had been hospitalised for psychiatric illness. Of 145 in the group with serologically diagnosed childhood CNS infections who had survived to age 16 years, 4 (2.8%) developed schizophrenia, compared with 0.7% of the unexposed majority. This 4-fold relative risk may even underestimate the true risk because of the restriction to severe exposure. An estimate of the population attributable fraction, i.e. the amount by which the population burden of schizophrenia would be reduced if the effect of the exposure, if causal, were removed, is around 4%. As with any causal inference, one must consider the possibility of reverse causality. The CNS may already have been abnormal in the individuals who developed infection and schizophrenia, and these abnormalities may have made them liable to CNS infection. Genetic or epigenetic factors as yet unknown may be necessary components of the causal pathway.

Prenatal infection: possible mechanisms and future directions

What are the possible etiological mechanisms underlying the association between prenatal exposure to infection and later schizophrenia? Brown et al (2000) offer a number of possibilities: hyperthermia, medication, and the maternal inflammatory response to infection (pro-inflammatory cytokines and chemokines) (Nelson et al, 1998). Immune mechanisms have also been suggested (Wright et al, 1999, Fatemi et al, 1999). The role of genetic vulnerability remains unclear (Murray et al, 1992).

These are all interesting possibilities. The availability of serum from birth cohorts in the US who are now in the period of risk for schizophrenia may help to answer some of these questions and test these hypotheses more precisely (Susser E et al, 2000). A new generation of studies on the prenatal infection and schizophrenia story is beginning. One striking finding has already emerged from examination of stored prenatal serum samples from the Providence cohort of the National Collaborative Perinatal Project. Buka et al (2000) found a strong association between maternal antibodies to herpes simplex virus type 2 gG2 glycoprotein and later psychosis (OR 5.8:1.7-19.3). The investigators also found an association between adult psychosis and maternal levels of certain cytokines, but these were preliminary results. The future almost certainly lies in the combination of molecular biological techniques to define exposure (Yolken & Torrey, 1995), molecular genetics to define susceptibility, and the opportunistic use of population-based samples.

2.2.3 Other putative prenatal risk factors

Prenatal Famine

A series of ecological studies of exposure to pre-natal famine (Susser & Lin, 1992; 1994; Susser E et al., 1996) have demonstrated dose-response relationships between maternal nutritional deprivation during the Nazi blockade of the Netherlands in the winter of 1944-45 and risk of later schizophrenia in the offspring. The initial finding to emerge from these studies was that birth cohorts exposed to the famine in early but not late gestation had a two-fold increase in risk for schizophrenia (Susser and Lin, 1992; Susser E et al, 1996). A subsequent study using military conscription data demonstrated that prenatal famine during early gestation was associated with a two fold elevation in risk for schizoid or schizotypal personality disorders (Hoek et al, 1996). The authors postulate that severe nutritional deprivation is the etiological mechanism involved (Hoek et al, 1999; Butler et al, 1999) and this intriguing possibility has received indirect support from a finding that a short interval between siblings is associated with an increased risk of schizophrenia (Westergaard et al, 1999). Again, there is biological plausibility for this putative cause; congenital central nervous system defects in this population were related to famine exposure in a similar fashion (Susser et al., 1985). Confounding and interaction with genetic effects are issues that the investigators are tackling by studying the individuals, and by more detailed studies of nutritional status in birth cohorts (Hoek et al, 1999).

Rhesus incompatibility

Rhesus incompatibility, characterized by an Rh-negative mother pregnant with an Rh-positive fetus, has been associated with an elevated risk for schizophrenia. Hollister et al (1996) used data on males from the Danish Perinatal Cohort and found an elevated risk for schizophrenia among offspring of Rh-incompatible pregnancies compared with Rh-compatible pregnancies. Rhesus incompatibility can give rise to haemolytic disease of the newborn that results, among other things, in childhood neuromotor abnormalities and behavioural disorders such as emotional instability. It is possible that schizophrenia is yet another, remote consequence of rhesus haemolytic disease (Hollister and Brown, 1999). Rhesus haemolytic disease occurs most commonly in mothers who have already delivered a Rh-positive child, thus triggering the production of the antibody against the Rh(D) antigen. As hypothesised, the risk for schizophrenia among males in the Danish Perinatal Cohort Study was increased over threefold in second and later-born offspring from Rh-incompatible pregnancies, but there was no increased risk for first born offspring (Hollister et al, 1996).

Prenatal stress

Psychosocial stress is accepted as playing a role in the precipitation of the adult schizophrenia syndrome (Steinberg and Durrell, 1968, Brown and Birley, 1968). Stress may also act early in life, even in the pre-natal period, and play a role in predisposition. A classic paper by Huttunen and Niskanen (1978) shows a greatly increased risk of schizophrenia (OR 6.2) among individuals whose father died before the child's birth compared with those whose father died in the first year after birth. This appears to provide evidence for the involvement of prenatal stress in the etiology of schizophrenia but, like the findings from the Dutch Hunger Winter cohort, these findings remain unreplicated.

The association between prenatal exposure to stress and schizophrenia is difficult to study but has been investigated in a series of ingenious ecological studies using population-based data on discrete, highly stressful events. VanOs and Selten (1998) demonstrated a small increased risk of schizophrenia among individuals in Holland who were in utero during the Nazi invasion in May 1940. Selten et al (1999) found an nonsignificant increased risk of psychosis (RR 1.8; 95% CI:0.9-3.5) among those exposed during gestation to the 1953 Dutch Flood Disaster. Kinney et al (1999) report a similar effect for prenatal exposure to a tornado in Worcester, Massachusetts.

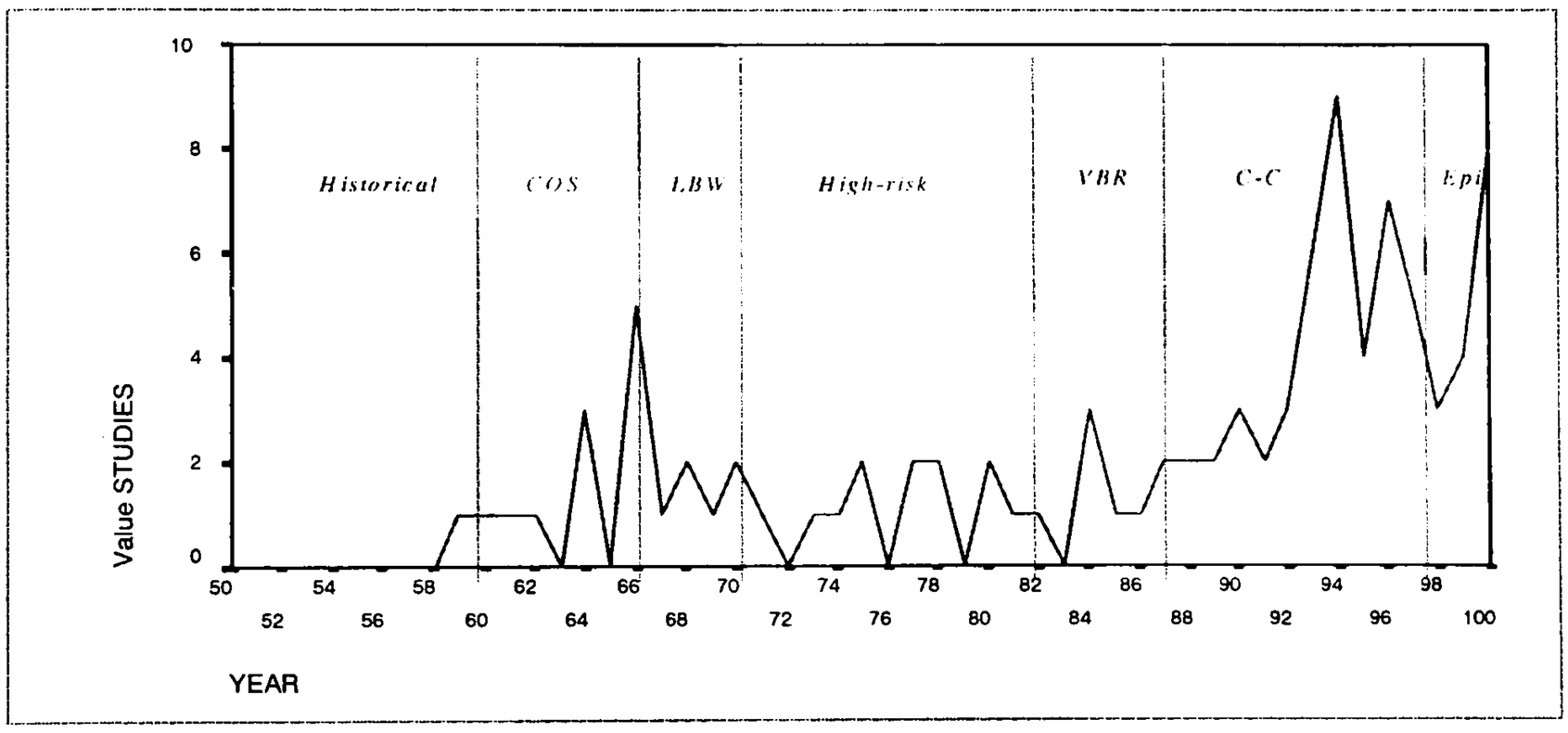
More subtle forms of prenatal stress may also have an effect. In the 1966 North Finland birth cohort, both maternal depression in late pregnancy (Jones et al, 1998) and "un-wantedness" of a pregnancy by the mother (Myhrman et al, 1996) were independently associated with a modest increase in the risk of schizophrenia in the offspring. The reasons for the pregnancy being unwanted were unknown, as was the attitude of the mother once the child was born. Many potential confounders such as maternal age, physical conditions and socio-economic status were taken into account, but a diluted genetic effect cannot be excluded. Mednick and Schulsinger (1968) reported from the Copenhagen High Risk study that 69% of the mothers of the high risk children who suffered severe early psychiatric breakdown were under severe stress (eg jailing of a husband) at the time of the pregnancy compared with 29% of the mothers of the 'well' high risk children. This finding implies an interaction between genetic vulnerability to psychosis and prenatal exposure to stress.

There is a considerable animal literature concerning the effects of prenatal stress on brain development and behaviour of the offspring (see Suomi 1997 for review) but unfortunately these effects are difficult to study in human subjects. The effect is thought to be mediated by glucocorticoid effects on the fetal hypothamalo-pituitary-adrenal axis.

2.3 Obstetric complications as risk factors for schizophrenia

The association between obstetric complications (OCs) and the risk of later schizophrenia has captured the imagination of investigators with a persistence and fervour unusual in psychiatric epidemiologic research. Investigation of these early risk factors has been crucial in promoting awareness of non-genetic etiological risk factors for schizophrenia and in furthering the idea of gene-environment interaction. In this chapter I outline the history of this substantial literature by dividing it into different phases (see Figure 2.1). I then summarise the current state of knowledge of these risk factors using meta-analytic techniques and discuss the conceptual problems with current approaches to obstetric complications.

Figure 2.1 Time trends in the publication of studies of OCs and schizophrenia



2.3.1 Historical review

The Historical Phase (1934-1959)

The first mention of an association between birth complications and schizophrenia occurred in the American Journal of Psychiatry in 1934. Aaron Rosanoff and colleagues published, 'The etiology of the so-called schizophrenic psychoses', based on a sample of 142 pairs of twins concordant and discordant for schizophrenia. The authors concluded from their detailed case reports that schizophrenia could be regarded (at least in part) as a 'decerebration syndrome which may result from birth trauma'. Possibly due to the intervention of the second world war, nothing further was published on this topic until Benjamin Pasamanick, and colleagues published

'Pregnancy experience and the development of behaviour disorder in children', again in the American Journal of Psychiatry in 1956, proposing their now-classic thesis of a 'continuum of reproductive casualty' , whereby pregnancy and birth complications can lead to a gradient of injury extending from fetal and neonatal death through cerebral palsy, epilepsy, mental deficiency and behaviour disorder. The authors emphasised that 'the associations occurred with the prolonged and probably anoxia-producing complications of pregnancy such as toxaemias and bleeding...rather than the mechanical factors of delivery." (Pasamanick et al, 1956; Pasamanick and Knobloch, 1960). The importance of pregnancy rather than delivery complications, and the issue of non-specificity were to be 'rediscovered' again many decades later.

The Childhood Schizophrenia phase (1962-1966)

Pasamanick's paper (Pasamanick et al, 1956) awakened interest in the relationship between obstetric complications and childhood schizophrenia. In 1966, the first review paper on the topic of OCs and schizophrenia appeared (Pollack and Woerner, 1966), which summarised five studies (Vorster, 1960; Knobloch and Pasamanick, 1962; Hinton, 1963; Taft and Goldfarb, 1964; Terris, 1964), and found consistently significant associations between complications of pregnancy and childhood psychosis (particularly toxaemia, bleeding and severe maternal illness). The authors noted the methological limitations of the studies, particularly the use of maternal recall as the main source of exposure information and concluded, "The need for further research employing large samples... is strongly indicated by these findings". However, rather than stimulating further research into OCs and childhood schizophrenia, this review seems rather to have put it to rest. It is likely that uncertainty about the diagnostic classification of childhood psychosis rendered such research difficult. After a gap of 10 years, Torrey et al (1975), published a paper based on prospectively recorded data, that reported a positive association between bleeding in early and mid-pregnancy and childhood psychosis, echoing the earlier conclusions of Pasamanick and Knobloch (1966).

The Low Birthweight phase (1966-1970)

In 1966, just as the interest in OCs and childhood schizophrenia was waning, Lane and Albee (1966) published an influential paper reporting an association between low birthweight and adult-onset schizophrenia. They reported that the birthweights of 52 hospitalised schizophrenic adults were significantly lower than those of 115 of their siblings, independent of prematurity. Although the results were significant, the difference between the mean birthweight of the cases and the mean birthweight of the average of the siblings was not great – in the region of 175g.

Few of the cases actually fell into the 'low birth weight' category (<2500g), but 70% of the cases weighed less than the average of the other children in the family. Therefore, there appeared to be a shift in distribution of birth weight within a population of cases compared with non-cases rather than an association between schizophrenia and an arbitrarily-defined category of 'low birth weight'. Sadly, this elegant concept of a 'shift in distribution' was not to re-emerge for many years (Jones and Done, 1997; Jones, 1999). A group of researchers from the Hillside Hospital, New York, (led by Margaret Woerner and Max Pollack), attempted to replicate the findings of Lane and Albee (1966), but they used smaller samples, with poorer quality obstetric data, and failed on the whole to find significant differences. (Pollack et al, 1966; Woerner et al, 1971, Woerner et al, 1973). Although reported as 'negative' studies, the magnitude of the difference in birthweight found between cases and siblings was very similar to that reported by Lane and Albee (1966).

The High-Risk phase (1970-1980)

The high-risk era began with an analysis of OC data from the Copenhagen High Risk Study (Mednick and Schulsinger, 1968). Mednick and colleagues (1970) found that 70% of the high risk children who were psychiatrically ill by their early twenties had suffered one or more serious pregnancy or birth complications compared with 15% of the high risk group who remained well and 33% of the control group. They speculated that, given a genetic predisposition, schizophrenia will only appear if the hippocampus is selectively injured by anoxia at birth – gene-environment interaction. Many interesting findings emerged from other high-risk studies over the next few years. Rieder et al (1977) reported an excess of bleeding and swelling during high-risk pregnancies. A striking excess of unexplained fetal and neonatal deaths among the offspring of schizophrenic parents was reported by a number of investigators (Sobel, 1961; Rieder, 1975; Modrewska, 1980). In 1967 Stabeneau and Pollin published an analysis of birth histories of 100 pairs of monozygotic twins discordant for schizophrenia and reported that significantly more of the schizophrenic (index) twins had been the lighter of the two at birth and had experienced birth complications, particularly asphyxia.

However a series of studies from Arnold Sameroff and Melvin Zax, (University of Rochester, NY) dealt the high risk stategy a severe blow. They found no differences between the birth histories of schizophrenic women and those of women with depressive neurosis, (Sameroff and Zax, 1973; Zax, Sameroff and Babigian, 1977), and postulated that "chronicity of mental disorder was more closely related to number of delivery complications than any particular psychiatric diagnosis." Although these studies were based on small numbers of schizophrenic women (12 and 29 respectively), they led to a loss of confidence in the high-risk strategy. This

was further compounded by a series of largely negative findings from other high-risk studies, (McNeil and Kaj (1973), Mirdal et al (1974), Cohler et al (1975); Hanson et al 1976). A review of the high risk literature by McNeil and Kaij in 1978 concluded that there was little evidence for an excess of obstetric complications in births to parents with schizophrenia. Although this conclusion was challenged two decades later by Sacker et al (1996), the high-risk era was virtually over by 1980. Indeed, only a handful of papers on the general topic of OCs and schizophrenia were published during the early 1980's, (Jacobsen and Kinney, 1980; Parnas et al (1982), DeLisi et al 1987). It may even have seemed then that no more would be heard on this topic – but this was not to be…

The Brain imaging phase (1984-85)

The application of new brain imaging techniques to data from the high risk and twin studies (Schulsinger et al, 1984, Reveley et al, 1984) provided the impetus for the next phase in the literature. The original CT scan studies showing cerebral ventricular enlargement in schizophrenia were originally thought to reflect neurodegeneration (Johnstone et al, 1976; Weinberger et al, 1982). However, Schulsinger et al (1984) reported increased ventricular size in those offspring of schizophrenics who had been exposed to obstetric complications, while Reveley et al (1984) noted that among normal twins, those who had been subject to OCs had larger ventricles than those who hadn't. Murray et al (1985) suggested that intraventricular haemorrhage of the newborn infant might be one cause of the ventricular enlargement found in schizophrenia and proposed a distinction for research purposes between familial (presumed mainly genetic) and sporadic (presumed mainly environmental) forms of schizophrenia.

The path to the 'neurodevelopmental hypothesis' of schizophrenia

In 1987 two research groups (one from the US and one from the UK) set forth similar ideas regarding a 'neurodevelopmental hypothesis' of schizophrenia, (Murray and Lewis, 1987; Weinberger et al, 1987). A central tenet of this theory was that schizophrenia can result from a disruption in the normal maturational processes of the brain – this disruption could be caused by a combination of genetic or environmental factors. The association between OCs and later schizophrenia was a crucial strand of evidence for this theory as it provided the only convincing candidate for an environmental etiological agent. A study by McNeil and Kaj (1978) using Swedish birth record data, published a decade earlier, which had found that 'process' schizophrenics had a significantly increased frequency of total OCs, was used as supporting evidence for this assertion.

The Case-Control phase (1987-1996)

In 1987, Lewis and Murray published a paper reporting that more patients with schizophrenia had obstetric complications (as noted in their psychiatric hospital records) than did patients with other psychiatric disorders. Subgroup analyses subdivided patients on the basis of family history, age at onset, poor premorbid personality, and cerebral ventricular size, and compared rates of OCs between the groups. (Lewis, et al 1989). The quest for 'subgroups' and the search for correlates of obstetric complications were themes that would recur many times during the years that followed. Another impact of this study was the introduction of the so-called 'Lewis-Murray' or 'Lewis et al' scale for rating retrospective information on OCs (Lewis et al, 1989). This scale was derived from a consensus of six previous scales, three from the obstetric and three from the psychiatric literature. The scale consists of 15 complications, and defined thresholds for rating some complications as 'definite' or 'equivocal'. This 'user-friendly' but 'atheoretical' scale dominated the OC literature for the next decade, and formed the basis of later meta-analyses (Geddes and Lawrie, 1994; Verdoux et al, 1997; Geddes et al, 1999). It was used for rating OC information from casenotes, birth records and maternal interview. The scale was partially validated by O'Callaghan et al (1990) when OC information from maternal interview obtained using the scale was compared with prospectively recorded birth records for 17 patients.

The combination of three factors: (1) the theoretical framework provided by the 'neurodevelopmental hypothesis', (2) the possibility of using maternal recall and casenotes as sources of OC information, and (3) the availability of an easy-to-use rating scale, gave rise to a veritable 'flood' of case-control studies in the first half of the 1990's investigating OCs and schizophrenia.

Sadly, the methodology in many studies was not optimal, and this frenzy of research activity served to confuse the issue rather than elucidate it. Some studies found a significant overall effect for OCs, (Eagles et al,1990; O'Callaghan et al. 1992; Verdoux and Bourgeois 1993; Gunther-Genta et al 1994, Hultman et al, 1997) others didn't (McCreadie et al.1992, Heun and Maier 1993). Different variations of the Lewis-Murray scale were used but the results were still presented as total scores. Some studies had no normal control group (Foerster et al.1991, Rifkin et al 1994 , Smith et al 1998), while others used sibling controls only, (Eagles et al. 1990; McCreadie et al, 1992; Heun and Maier, 1993; Gunther-Genta et al 1994; Willinger et al, 1996). Although some of the studies clearly attempted to use population-based cases and/or controls, (McNeil and Kaij, 1978; Eagles et al, 1990; O'Callaghan et al, 1992; Hultman et al, 1997), the final samples were selected to a varying degree and prone to bias, (Geddes and Lawrie, 1995).

Many studies relied solely on maternal recall as the source of information about the exposure, (McCreadie et al (1992; Verdoux and Bourgeois, 1993; Rifkin et al, 1994). Studies that found no significant overall effect for OCs carried out subgroup analyses: OCs were examined in relation to family history (O'Callaghan et al, 1990; Foerster et al, 1991; McCreadie et al, 1992; McNeil et al, 1993, Kunugi et al, 1996a), premorbid adjustment (Foerster et al, 1991), imaging abnormalities, (Owen et al, 1988, Smith et al, 1998); age at onset (O'Callaghan et al, 1990; O'Callaghan et al, 1992; Kirov et al, 1996, Nicholson et al, 1999), gender (O'Callaghan et al, 1992; McNeil et al, 1993; Kirov et al 1996, Kunugi et al, 1996a), neurological abnormalities (O'Callaghan, 1990, McCreadie et al, 1992), ethnicity, (Hutchinson et al, 1997), and season of birth (McNeil et al, 1993), among others. Unfortunately there was little consistency in the results from these 'subgroup' analyses. The search for environmental risk factors for schizophrenia had become an example of 'circular epidemiology', namely "..the tendency to perseverate at one level of evidence, for example, on one type of study design without moving forward' (Kuller, 1999).

The end of an era

In 1995, Geddes and Lawrie (1995) carried out a meta-analysis of published results from 16 case-control studies and 2 cohort studies, and reached three important conclusions: (1) A pooled odds ratio of 2.0 (CI 1.6-2.4) suggested that OCs were modestly associated with schizophrenia (2) There was evidence for selection and publication bias in the OC and schizophrenia literature, with a notable deficit of small negative studies, (3) There was significant heterogeneity between the results from the case-control studies and the two birth cohort studies published at that time. So, some good news and some bad news, there may be an effect – but then again it could be due to selection bias or some other aspect of study design. However, Geddes and Lawrie (1995) concluded their review on an optimistic note: "*Future studies should have sample sizes that are large enough to provide sufficient power to quantify risk estimates for individual, rigorously-defined OCs and to be able to adjust the estimates for the effect of potential confounding factors*". And that is exactly what happened next – the next phase of the literature began.

The 'population-based' studies (1997-present)

The 'population-based ' phase of the OC and schizophrenia literature began in about 1997 (although two studies published before that time are included) and continues to date (McNeil, 1995). They all have the following characteristics: large and psychiatrically well-defined schizophrenic samples drawn from population-based registers; use of standardised, prospectively-collected obstetric information from birth records or registers; general population

control subjects with OC information from the same source and context; control of demographic confounding factors through either matching or statistical adjustment. Investigators now usually report odds ratios for all individual OCs recorded on the birth records. Details of the designs and results of these 'population-based' studies are given in Table 2.1. Somewhat surprisingly, it can be seen that these methodological advances have not confirmed the earlier findings. Although the designs of these studies are broadly similar their results are quite diverse and no consensus has yet been reached. I will explore the reasons for this in the remainder of the chapter.

Table 2.1 Summary of findings from population-based studies of obstetric complications and schizophrenia

Study	Findings
Done et al (1991)*	No overall association between risk factors for perinatal death and later schizophrenia. Low maternal weight and medications given to baby were associated with narrowly-defined schizophrenia.
Buka et al (1993)	Non-significant increased risk of psychosis in those exposed to chronic fetal hypoxia (OR 2.6)
Sacker et al (1995)	Re-analysis of Done et al (1991). The following variables were associated with increased risk of narrowly-defined schizophrenia: low maternal weight, Maternal psychological problems, smoking in pregnancy, poor antenatal attendance, rhesus negative, parity >2, previous births <2500g, bleeding in pregnancy, untrained person delivering, baby's weight <2500g, other drugs given to baby.
Jones et al (1998)	Low birth weight (OR 2.4:1-5.6), combination of low birth weight and prematurity (OR 3.5:1.3-9.6) and perinatal brain damage (OR 6.9:2.9-16.3) were associated with schizophrenia
Hultman et al (1999)	Schizophrenia was associated with multiparity (OR 2.0); bleeding during pregnancy (OR 3.5); winter birth (1.4); small for gestational age (males only OR 3.2); parity >4 (males only OR 3.6)
Dalman et al (1999)	Increased risk of preeclampsia (OR2.5); vacuum extraction (1.7); malformations (2.4), parity=1 (1.3); bleeding during pregnancy (2.0); threatened premature delivery (2.3); gestational age <32weeks (2.7); prolonged delivery (1.6); uterine inertia (2.4; ponderal index<20 (3.4),respiratory illness (1.5). birthweight <2500g (males only 2.2); birthweight <1500g (females only 6.0); SGA (males only 1.9) Preeclampsia remained significant after adjusting for all other complications.
Kendell (1) et al (2000)	No association found between any obstetric complication and schizophrenia.
Kendell (2) et al (2000)	Emergency caesarian section (OR 3.7:1.02-13.1) and labour >12 hours were associated with later schizophrenia.
Byrne et al (2000)	No overall differences in rates of OC. Caesarian section and narrow maternal pelvis commoner among cases. Early-onset males had greater frequency and severity of OCs than controls.
Cannon et al (2000a)	>3 hypoxia-related complications increased the risk of schizophrenia (OR 3.84) and particularly early-onset schizophrenia (OR 7.3).
Rosso et al (2000)	Risk of early-onset schizophrenia increases (OR 2.16:1.3-3.5) per hypoxia-related OC.
Zornberg et al (2000) *	Re-analysis of Buka et al (1991). Composite variable entitled 'hypoxic-ischaemia-related fetal/neonatal complications' associated with schizophrenia (OR 4.56:2.42-8.6)
Dalman et al (2001)	Signs of asphyxia at birth were associated with increased risk for schizophrenia (OR 4.4:1.9-10.3) after adjusting for other complications and confounders.

2.3.2 A meta-analytic review of the population-based studies

The standardised fashion of reporting results and the methodological similarities of the population-based studies lend themselves to meta-analysis. Meta-analysis provides a method for integrating quantitative data from multiple studies by using a weighted average of the results in which larger studies have more influence than smaller studies. The advantages of meta-analysis are that it improves the estimates of effect size and increases the statistical power, (Fleiss and Gross, 1991). This meta-analysis has been carried out as a means of summarising the large amounts of data available in the recent population-based studies and in an effort to make sense out of studies with conflicting conclusions. The meta-analysis should be viewed in the context of the historical review and is not a 'stand-alone' analysis in itself. Most, but not all, of the recommended criteria for reporting meta-analyses of observational studies in epidemiology (MOOSE) have been fulfilled (Stroup et al, 2000).

Method

Inclusion criteria: Studies were included in the meta-analysis if they fulfilled the following criteria (1) well-defined schizophrenic samples drawn from population-based registers or cohorts; (2) use of standardised, prospectively-collected obstetric information from birth records or registers, (3) control subjects drawn from the general population with OC information from the same source and context and (4) data on individual obstetric complications presented in a standardised format that allowed comparisons between studies (Egger et al, 1997).

Search strategy: Studies used in the meta-analysis were identified by search of computerised databases, search of the reference lists of studies identified for inclusion, and contact with fellow researchers in this field at international meetings. Eight studies were identified that fulfilled all criteria and these are described in Table 2.2 (Sacker et al, 1995; Jones et al, 1997; Hultman et al, 1999; Dalman et al, 1999; Kendell et al, 2000; Byrne et al, 2000; Dalman et al, 2001). Two studies were presented in one paper (Kendell et al, 2000). A further 5 studies were identified that fulfilled the first 3 criteria but not the 4th as the obstetric data was presented in aggregate form and could not be used in this analysis, (Done et al, 1991;Buka et al 1993; Cannon et al, 1999; Rosso et al, 2000; Zornberg et al, 2000a). The studies not included in the meta-analysis are mentioned in the discussion of the results where appropriate.

Statistical analysis: Meta-analyses were performed in STATA 6.0 (StataCorp., College Station, Texas), using the 'meta' command (Sharpe and Sterne). The 'meta' command provides pooled estimates, confidence limits and a test that the true pooled effect is zero, obtained from fixed and random effects meta-analysis. Individual obstetric complications were included in the analysis if more than two studies reported on that complication in a comparable way. Odds ratios and 95% confidence interval were extracted from each paper and used in the analysis. For cohort studies the adjusted odds ratios were used in the analysis. A fixed effects pooled estimate is presented for each complication. The fixed effects model assumes that variability between studies is due to random variation (Egger et al, 1997). Two of the studies, Hultman et al (1999) and Dalman et al (1999), actually report on the same dataset, though with different sampling frames, and the Dalman et al (1999) study has the larger number of subjects. Therefore to avoid overlap, where both studies report on the same obstetric complication, the measure of effect from the Dalman et al (1999) study is used, and the Hultman et al (1999) finding is omitted. For each complication, a homogeneity statistic Q was obtained. A significant value of Q indicates that there is heterogeneity between the studies for that complication. However since the maximum number of contributory studies never exceeded 6, there was not sufficient power to formally investigate potential sources of heterogeneity in study findings. Where significant heterogeneity was detected, a random effects estimate was also presented. The random effects model assumes a different underlying effect for each study and leads to wider confidence intervals than the fixed effects model. A funnel plot was examined and showed no evidence for publication bias.

Results

Results of the meta-analysis for the individual complications are presented in Table 2.3. Significant differences between cases and controls were found for the following variables in order of significance (OR:95% ci): uterine atony, (2.2:1.5-3.5); bleeding in pregnancy, (1.7:1.1-2.5); asphyxia, (1.7:1.2-2.6); emergency caesarian section, (3.2:1.4-7.5); birthweight <2000g, (3.9:1.4-10.8); birthweight <2500g, (1.7:1,2-2.3); congenital malformations, (2.3:1.2-4.6); diabetes in pregnancy, (7.8:1.4-43.9); rhesus variables (2.0:1.01-3.96) (which includes rhesus incompatibility, rhesus negative mother, rhesus antibodies), pre-eclampsia, (1.4:0.99-1.85). Significant heterogeneity was detected for two of these complications: asphyxia, and birthweight <2500g. Random effects estimates for these complications were: 2.01 (0.7-5.5:p=0.17) and 1.66 (0.94-2.95:p=0.08) respectively. Because of the small numbers of studies contributing to each estimate, (3 and 5 respectively), potential sources of heterogeneity (such as age of onset, gender or period effects) were not formally examined. Three complications just missed formal statistical significance: placental abruption, (4.02:0.9-18.1), head circumference <32 cm (1.3:0.8-2.06); and a negative association with non-spontaneous delivery, (0.6:0.4-1.01).

Table 2.2 Summary of studies included in the meta-analysis of obstetric complications and schizophrenia

Study	Country	Type	No. cases	No. control	Variables for matching or adjustment	Diag. criteria	Birth years	Age range cases	% ♀	Source of cases	Source of obstetric info.	Power*
Sacker et al (1995)	UK	Coh.	35	16812	N/A	PSE /S+	1958	16-28	39	Mental Health Enquiry '74-86	Midwife report	40 (10)
Jones et al (1997)	Finland	Coh.	76	1074	Adjusted for: sex, social class, mat. depression and smoking	DSM-III-R	1966	27-28	33	Hospital Discharge Register to 1993	Midwife report	50
Hultman et al (1999)	Sweden	C-C	167	835	Matched on: child's sex, yob, hospital of birth.	ICD-9	1973-79	15-21	35	Hospital Discharge Register '87-'94	Birth register – obs.	80 (35)
Dalman (1) et al (1999) **	Sweden	Coh.	238	507278	Adjusted for child's sex, yob, hosp. And maternal marital status, age, hx of psychosis	ICD-9	1973-77	15-22	41	Hospital Discharge Register '87-'95	As above	95 (55)
Kendell (1) et al (2000)	Scotland	C-C	296	296	Matched on sex, dob, hosp, SEG, maternal age,parity	ICD-9, ICD-10	1971-74	22-26	24	National Hospital Admission Register to 1996	Birth register-obs or midwife	78 (30)
Kendell (2) et al (2000)	Scotland	C-C	156	156	As above	ICD-9, ICD-10	1975-78	18-21	24	National Hospital Admission Register to 1996	As above	50 (15)
Byrne et al (2000)	Ireland	C-C	431	431	As above	ICD-9	N/S	N/A	41	Dublin Psychiatric case register 1972-92	Labour ward records	92 (45)
Dalman (2) et al (2001) **	Sweden	C-C	524	1043	Matched on sex,hosp., yob, parish. Adjusted for mat. hx psychosis, mat. Age, parity, SEG, marital status, attendance at a/n care	ICD-8 ICD-9	N/S	Mean 29.5 yrs,	34	Stockholm county inpatient register '71-94	Birth records: obs or midwife	99 (68)

*Power to detect an odds ratio of 2.0 with 95% confidence for an exposure with a prevalence of 10% among controls. (Power to detect an odds ratio of 1.5)

**Final analysis also adjusted for other obstetric complications. This estimate was not used in the meta-analysis.

Table 2.3 Comparison of obstetric complications in cases and controls in 8 studies

Complication	No. studies	No. cases exposed	Total no. cases	No. control exposed	Total no. controls	Fixed Pooled estimate (95% CI)	P value	Q
Pre-eclampsia	6	75	1712	18286	510275	1.3 (0.99-1.9)	**0.05**	8.5
Bleeding in pregnancy	6	34	1223	9367	524972	1.7 (1.1-2.5)	**0.009**	9.2
Rhesus variables	3	18	759	2911	17537	2.0 (1.0-3.9)	**0.047**	1.1
Diabetes in pregnancy	2	3	237	3	1909	7.7 (1.4-44)	**0.021**	0.0
Anaemia in pregnancy	3	20	522	96	1526	1.2 (0.7-2.3)	0.45	4.4
UTI in pregnancy	3	20	690	7115	507730	0.8 (0.5-1.6)	0.625	2.8
Threat. prem. delivery	2	8	308	6498	508352	1.9 (0.8-4.9)	0.141	0.1
Placental abruption	2	3	308	1643	508352	4.02 (0.9-18)	**0.07**	2.2
Smoking in pregnancy	2	26	105	5752	17886	1.3 (0.9-2.1)	0.158	0.6
Induction	4	186	689	232	2361	1.2 (0.9-1.6)	0.252	0.7
Uterine atony	2	27	659	16913	507703	2.3 (1.5-3.5)	**0.000**	0.2
Caesarian section	5	63	1214	42947	526045	0.99 (0.7-1.4)	0.978	5.5
Emergency CS	3	20	818	1595	507863	3.2 (1.4-7.5)	**0.006**	0.1
Forceps or vacuum	7	124	1724	29753	527058	1.1 (0.8-1.4)	0.478	8.5
Non-spontaneous delivery	2	46	331	1554	17108	0.6 (0.4-1.0)	**0.058**	0.0
Cephalopelvic disprop.	2	10	662	42	2338	1.0 (0.3-3.8)	0.95	2.1
Non vertex presentation	6	74	1667	61130	510208	0.9 (0.7-1.2)	0.45	4.4
Breech delivery	3	11	464	13580	508508	0.8 (0.4-1.9)	0.738	0.4
Cord around neck	2	171	893	333	1345	1.03 (0.8-1.3)	0.83	0.17
Asphyxia	3	60	1109	119	2297	1.7 (1.1-2.6)	**0.008**	10.1*
Congenital malformations	3	10	737	6144	508781	2.3 (1.2-4.6)	**0.012**	0.53
Apgar <7 at 1 minute	2	18	390	22771	507434	1.1 (0.6-1.9)	0.758	0.45
Child stayed in hosp.	3	110	973	99	1488	1.07 (0.8-1.4)	0.65	6.7*
Birthweight <2500g	5	60	1294	19343	536045	1.7 (1.2-2.3)	**0.002**	12.5*
Birthweight <2000g	2	6	504	78	10926	3.9 (1.4-10.8)	**0.009**	2.3
BW<2500g &prem.	4	41	954	215	11376	0.9 (0.6-1.5)	0.84	7.3
SGA	5	86	1272	23485	519229	1.2 (0.9-1.6)	0.19	3.2
Gestational age <37wks	5	67	1290	21710	536051	1.2 (0.9-1.6)	0.2	0.2
Gestational age >42wks	3	34	1187	16065	508747	1.1 (0.7-1.7)	0.72	2.2
Head circ.<32cm	2	53	758	15388	508315	1.4 (0.9-1.9)	**0.08**	0.01
Head circ.>38cm	2	37	758	12617	508315	1.3 (0.8-2.1)	0.38	0.02
Length <49cm	3	130	761	105205	51320	1.06 (0.8-1.3)	0.59	0.17

*p<0.05

Discussion

The significant estimates from the meta-analysis appear to group into three main categories:

(1) Complications of pregnancy

(2) Abnormal fetal growth and development

(3) Complications of delivery

Complications of pregnancy: (bleeding, diabetes, rhesus incompatibility, pre-eclampsia).

Bleeding during pregnancy has been associated with schizophrenia since the earliest days (Pasamanick et al. 1956, Rieder et al, 1977; Torrey et al 1975). Unfortunately there is little information from studies about the timing and amount of bleeding which would help elucidate the mechanism involved (Scott, 1972). Similarly, pre-eclampsia has long been postulated as a risk factor for schizophrenia but the putative mechanism is not clear. In 1996 Kendell and colleagues found an odds ratio of 9.0 for the association between preeclampsia and later schizophrenia– much larger than any effect previously reported. However in attempting to extend this sample and replicate this finding, a flaw in the original study design was uncovered that led to a retraction. (Kendell et al, 2000). Nevertheless, there was a significant association with pre-eclampsia in the largest 'population-based' study (Dalman et al, 1999), published to date. There has been much speculation about the possible mechanism of action of this association. The most popular theory at present involves the mechanism of abnormal fetal blood flow resulting in fetal hypoxia or malnutrition. Buka et al (1993) examined the risk of later psychiatric illness in relation to 'chronic fetal hypoxia', an aggregate variable which included severe and prolonged preeclampsia, and found a (non-significant) elevated risk of psychosis (OR 2.6).

The positive association between diabetes in pregnancy and later schizophrenia is based on only 2 studies in this analysis and there is no information on the type of diabetes involved. The effects on the developing brain of altered glucose metabolism are not well understood (Eriksson, 1995), though it is known that poorly controlled maternal diabetes is associated with an increased risk of impaired intellectual and psychomotor development, congenital anomalies and even fetal death in offspring (Schaefer et al, 2000). The association between schizophrenia and insulin-dependent diabetes mellitus could be explained by an autoimmune mechanism (Wright et al, 1996; Gilvarry et al. 1996), but whether this is of relevance is not known.

Autoimmune mechanisms could also be implicated in the association between rhesus incompatibility and later schizophrenia. Rhesus haemolytic disease of the newborn represents an illness with neurological consequences that is secondary to effects of a maternal antibody, (Hollister and Brown, 1999; Strauss, 1999) Haemolytic disease can lead to early spontaneous abortion, chronic fetal hypoxia, neonatal asphyxia and pulmonary edema, neonatal hyperbilirubinemia and kernicterus, (Hollister and Brown (1999). As discussed earlier in this chapter, the association has independent support from a cohort study that found a two fold increased relative risk of schizophrenia among men from rhesus incompatible pregnancies (Hollister et al,1997). Dalman and Cullberg (1999) found that neonatal hyperbilirubinemia is a risk factor for later mental illness but did not have sufficient power to examine schizophrenia separately.

Abnormal fetal growth and development: (low birthweight, congenital malformations, reduced head circumference)

Low birthweight has been associated with schizophrenia throughout each era of investigation. (Rosanoff, 1934, Pollack and Woerner, 1966, Lane and Albee 1966 , Mednick et al, 1971; Sacker et al., 1996; Stabeneau and Pollin 1968, Geddes et al, 1999). However this association is not invariably found (Ichiki et al, 2000), and there was significant heterogeneity in the estimate for birthweight < 2500g in this meta-analysis. The concept of a 'population shift' in birthweight, previously discussed, may account for this heterogeneity. Accordingly, studies that use an 'arbitrary' cut-off point for low birth weight (usually <2500g) will find inconsistent associations depending on the power of the study. A more useful approach is to use a quantitative analysis. A Finnish cohort study (Wahlbeck et al, 2001) has found that the risk of schizophrenia decreases in a linear fashion with increasing birth weight (OR 0.67 per kg, p=0.03), with similar inverse linear relationships with length at birth (OR 0.89 per cm, p=0.009) and placental weight (OR 0.13 per kg, p=0.01). No association was found between schizophrenia and prematurity, indicating that the low birth weight is due to intrauterine growth retardation. There are many causes of intrauterine growth retardation – almost any factor adversely affecting the fetus will retard its growth, and women with schizophrenia, or who later develop schizophrenia, have been shown to be at increased risk of behaviours during pregnancy associated with low birthweight outcomes, (Sacker et al, 1996; Bennedsen, 1998). We may therefore be dealing with a proxy variable for adverse genetic or intrauterine influences (or both) on the developing fetus. The association between reduced head circumference and schizophrenia, (first reported by McNeil et al, 1993,

and replicated by Kunugi et al, 1996), provide further support for an abnormality of fetal growth and development in schizophrenia but no clues about the underlying cause. The increased rate of congenital malformations found in this meta-analysis echoes the extensive literature on minor physical abnormalities and schizophrenia, (Lane et al, 1997, McNeil et al, 2000b), and implicates pregnancy as a time when potential etiological factors may be operating.

Complications of delivery: (asphyxia, uterine atony, and emergency caesarian section).

The most likely common mechanism of action for these delivery complications appears to be through fetal hypoxia or anoxia. This is not a new idea, (Pasamanick et al 1959, Geddes et al 1999). Putative hypoxia-related complications have been related to brain structural abnormalities among schizophrenic patients, (Cannon et al, 1993; McNeil et al, 2000b). Two cohort studies by Tyrone Cannon's group from the US and Finland respectively, found that a group of hypoxia-related obstetric complications significantly increased the risk of early-onset schizophrenia, (Cannon et al, 2000a; Rosso et al, 2000a), and the siblings of schizophrenics in both studies were no more likely to experience these complications than cohort members without schizophrenic siblings. Cannon and colleagues have proposed a model of schizophrenia involving interaction of genetic vulnerability and obstetric complications (Cannon, 1997) and further suggest that the neurotoxic effect of fetal hypoxia leads to an early onset of schizophrenia due to premature cortical synaptic pruning (Cannon et al, 1999; Rosso et al, 2000). Zornberg et al (2000a) carried out a re-analysis of the Buka et al (1993) dataset that found an increased risk of later schizophrenia and nonaffective psychosis in individuals who experienced 'hypoxic-ischaemia-related fetal/neonatal complications'. The authors created a complex, composite variable to represent this risk factor that seems to encompass all the three categories of complications found in this meta-analysis.

The major difficulty with proposing hypoxic-ischaemic damage as a causal risk factor for schizophrenia is that it is difficult to establish its independence: it may be related to pre-existing problems with the fetus (Goodman, 1988) or characteristics of the mother (Sacker et al, 1996, Bennedsen, 1998). Pre-existing fetal abnormalities can increase the incidence of various birth complications, including birth asphyxia (Nelson and Ellenberg, 1986). Investigations by McNeil et al (1996, 1999) found no empirical support for the position that LDC's are a simple reflection of pre-existing fetal abnormality (as measured by neonatal neurological abnormality and minor physical anomalies). Few studies have had the power to look at the interrelationships between

various obstetric complications in the same individuals. One exception is the study by Dalman et al, (2001), which found that the only complication that remained significant after adjustment for other obstetric complications and confounders was asphyxia, implying some independent effect for this complication. A large individual-patient data meta-analysis could throw some further light on this issue.

Limitations of meta-analysis

The limitations of using a meta-analytic approach for observational studies should be mentioned (Shapiro, Egger et al, 1998). Meta-analysis of randomised controlled trials is based on the assumption that each trial provides an unbiased estimate of an experimental treatment, with the variability of the results between the studies being attributed to random variation. However observational studies yield estimates of association that may deviate from true underlying relationships beyond the play of chance due to the effects of confounding or bias (Egger et al, 1998). Meta-analysis is no defence against such factors (Crow, 2000). The population-based studies in this meta-analysis, were relatively free from bias, and the odds ratios in the analysis were adjusted for confounders such as sex , hospital of birth and social class. However, the studies are drawn from different populations, in terms of geography, cohort and period effects, and age of onset. Measurement of obstetric exposures is highly dependent on the quality of the birth record information available. Obstetric practices and the nomenclature and meaning of different complications vary between countries and over time. For example 'uterine inertia' is a Scandinavian concept not mentioned in birth records from the UK or USA. Another problem is that many complications are not recorded in sufficient detail to give useful etiological information: bleeding during pregnancy is mentioned in many studies but there is usually no information on timing or amount of bleeding. Equally, it is often unclear whether caesarian section was an elective or emergency procedure. The problems inherent in this field of study can be illustrated by examining two large studies based on broadly the same dataset and with similar methodology, but which find different, even contradictory, associations between various obstetric exposures and schizophrenia (Hultman et al 1999; Dalman et al 1999). As discussed previously with regard to prenatal infection, methodological problems such as confounding or bias can have a major influence on study results especially when one is dealing with small relative risks on the threshold of detectability.

A comparison of this meta-analysis with another on the same topic but based on different groups of studies (Geddes et al, 1999) illustrates the effects of such methodological factors. Geddes et al (1999) carried out an individual patient data meta-analysis of 12 case-control studies that had used the Lewis-Murray scale to rate the exposure. Individual component case-control studies were based on treatment samples with frequent use of sibling controls, and exposure information was often obtained by maternal recall and, as a result, were prone to various types of bias. Significant associations were found between schizophrenia and premature rupture of membranes, gestational age shorter than 37 weeks, use of resuscitation or incubator, and birthweight <2500g. Studies using birth record data found a significant association with pre-eclampsia while the studies based on maternal recall found a significant association with forceps delivery, indicating that agreement between birth records and maternal recall varies for different categories of birth complications (Cantor-Graae et al (1998). Mothers may be less reliable historians for events occurring during pregnancy than for delivery problems. Thus there is little overlap with the results of our meta-analysis with agreement on only two associations: birthweight <2500g and pre-eclampsia. This lack of consensus is most likely to be due to methological differences between the component studies in the meta-analyses.

Problems with current approaches

a) Statistical power

Statistical power is a crucial issue in interpreting the results of studies of OCs and schizophrenia. The meta-analysis of Geddes et al (1999) with 700 cases and 835 controls had 90% power to detect an OR of 2.0 at a population prevalence of 5% but only 44% power to detect an OR of 1.5. As shown in Table 2.2 many of the cohort studies did not have sufficient statistical power to detect an odds ratio of 2.0 for an obstetric exposure with a population prevalence of 10%. These figures are actually conservative. Many obstetric complications occur at population prevalence of less than 10% and reported effect sizes are often less than 2.0. The differences in results between two large studies based on broadly the same dataset and with similar methodology, but which find different, even contradictory, associations between various obstetric exposures and schizophrenia, (Hultman et al 1999; Dalman et al 1999) are likely to be due to differences in statistical power between the two studies. In a sense the study of obstetric risk factors for schizophrenia is a search for rare risk factors for a rare disease and is thus suitable neither for the classical cohort or case-control designs. A combination of methods, such as the 'nested' case-

control design (Hultman et al, 1997, Dalman et al, 2001) is more useful but even so Table 2.2 shows that at best the power of the largest studies to detect odds ratios of 1.5 was less than 70%.

The issue of interactive effects is even more problematic. Pregnancy, birth and neonatal complications do not act independently of each other. Pregnancy factors that have been associated with schizophrenia, such as rhesus incompatibility and prenatal stress can increase the risk for hypoxic-ischaemic damage during delivery. Current studies have negligible statistical power to detect such interactive effects. The issue of gene-environment interaction will be discussed later.

b) Lack of information on the prenatal period

Birth records record the delivery and neonatal period in detail but information about prenatal exposures is usually retrospective taken at the time of admission to the labour ward, (McNeil, 1988; McNeil, 1995). Major pregnancy complications, such as pre-eclampsia are usually mentioned but there may be no mention of other complications such as prenatal stress or insufficient detail about timing of complications such as infection or bleeding. Nevertheless the meta-analysis reported in this paper shows that prenatal factors (even with the less-than-optimal data available) are associated with later schizophrenia. It is likely that even stronger effects would be found if detailed accurate data were available on the prenatal period. There is a great deal of evidence for prenatal risk factors for schizophrenia: including prenatal infection, prenatal malnutrition and prenatal stress, and this literature has been reviewed earlier in this chapter. Such exposures should ideally be incorporated into future studies of obstetric complications and schizophrenia. Another approach would be to follow up a cohort of individuals who have suffered definite specific prenatal (or perinatal) complications and assess a range of outcomes during development. This approach has already been useful in elucidating some rare prenatal exposures such as rubella infection (Brown et al, 2000) and Rhesus incompatibility (Hollister et al, 1996) and is currently being applied to follow-up studies of low birth weight and premature infants (Stewart et al, 1999).

c) Poor definition of obstetric complications

There are so many discrete exposures wrapped up in the term 'obstetric complication', that it is essentially meaningless to consider them as one risk factor (Zornberg et al, 2000b). There are many distinct associations to be considered in terms of chance, bias or confounding, before beginning to judge how any association, should be interpreted - causal or not. If the field is to

progress, it is not only in terms of population-based methods but also in terms of sharpening up our views of the exposures under scrutiny. As such a broad definition of OCs should no longer be used, as it will not progress our understanding of the field any further. Interestingly no-one realised initially just how common the broadly defined category of 'Lewis-Murray' type OCs are in the general population (about 25-30%, see Jones et al, 1997, Cannon et al, 1997). Greater definition of the exposure, (ie prenatal measurement of maternal antibodies), or quantitative measures (ie birth weight, head circumference) are likely to show larger and more consistent effects.

Some studies try to overcome the problems of definition of exposure and low statistical power by examining only one exposure based on a prior hypothesis, and this has proved a relatively fruitful endeavour, showing significant effects for the putative risk increasing mechanism of hypoxic/ischaemic damage (Buka et al. 1993; Cannon et al 2000; Rosso et al 2000; Zornberg et al. 2000a, Dalman et al, 2001) The main problem here is that no two sets of researchers have used the same combinations of exposures. This makes direct comparisons or pooling of the results difficult, and hinders replication.

d) Timing of exposure

As with infections, the period of risk during which hypoxic brain damage may lead to later schizophrenia appears to extend beyond birth. In the North Finland 1966 cohort, a group of CNS insults which had hypoxia as a common mechanism was identified and termed 'Perinatal Brain Damage' (PBD) (Rantakallio et al., 1987). This exposure has been used to investigate possible causes of mental handicap and childhood epilepsy. Given this link with other developmental CNS disorders, there was an a priori hypothesis for an association with schizophrenia. Of 125 survivors of PBD, 6 (4.8%) developed schizophrenia in adult life - a seven-fold relative risk (Jones et al., 1998). The estimate of the proportion of schizophrenia in the general population that may be attributable to this mechanism was 5-8% in this study.

e) Specificity

The specificity of these obstetric exposures for schizophrenia has not been established (Tarrant and Jones, 1999). It is possible that other mental disorders, such as affective disorders, have similar obstetric risk factors, but these have not been investigated to the same extent. I do not advocate repeating the whole cycle of investigation again for other disorders, but recommend including them as additional groups in the investigation of mechanisms. Another approach, as

mentioned earlier would be to follow up a cohort of individuals who have suffered certain pre and perinatal complications and assess a range of outcomes during development – a return to the approach advocated by Pasamanick and colleagues many decades ago (1956).

2.4 General discussion and conclusions

Investigation of the role of prenatal and perinatal risk factors in the genesis of schizophrenia provides a good example of the development of epidemiological thought and methodology over the last 40 years, beginning with ecological studies, then progressing through case-control studies, to general population cohorts and enriched samples where specific exposures are identified. What conclusions can be drawn from the large literature reviewed in this chapter?

It seems that many pre and perinatal risk factors are somehow involved in increasing the risk for schizophrenia in later life (see Table 2.4). Those with the best evidence to date are: prenatal (probably second trimester) exposure to influenza and other respiratory infections, prenatal rubella, hypoxia-related obstetric complications and low birth weight/fetal intrauterine growth retardation. Evidence is less secure for prenatal stress or prenatal malnutrition, principally because of the difficulties in obtaining suitable samples in which to examine these exposures.

Confounding and proxy variables

Investigations of pre and perinatal risk factors for schizophrenia are haunted by the ghost of residual confounding. The association with prenatal infection could be confounded by fever or medication. The association with hypoxia-related birth complications could be confounded by earlier prenatal factors or sociodemographic factors. The precise nature of these early risk factors is often unclear and interpretation of the etiological mechanism involved is difficult. In the case of season of birth, urban birth or immigation, one is dealing with a 'proxy' variable that encompasses many even smaller unknown risk factors, possibly interacting with each other to produce an effect. Current approaches do not easily allow us to explore these issues further, other than just to report an association, and these problems can never be resolved within the framework of a uni-level, risk factor model. As a result, investigations of pre and perinatal risk factors for schizophrenia have become 'stuck' at this point, reporting risk factors of vanishingly small effect over and over again – an example of circular epidemiology (Kuller, 1999). In epidemiological research in general, it has

been postulated that the 'vogue' for risk factor epidemiology is reaching the limits of its usefulness (Tauber 1995; Susser M, 1998; Fearon et al, 2001) and that other approaches which incorporate, but are not restricted by the traditional individual risk factor approach should also be utilised (Susser M & Susser E, 1996, Schwartz et al, 1999). These approaches are discussed in chapter 6.

Table 2.4 Estimate of approximate effect sizes for pre and perinatal risk factors for schizophrenia, (references in text)

Pre or perinatal risk factor		**Approximate effect size**
Category	**Specific risk factor**	**(RR or OR)**
Place or time of birth	Winter birth	1.15
	Urban birth	1.5-2.4
Infection	Prenatal Influenza	2.0
	Prenatal Respiratory infection (2°)	2.1
	Prenatal Rubella	5.2
	Neonatal and childhood CNS infection	4.0
Malnutrition	Prenatal famine (1°)	2.0
Prenatal stress	Bereavement of spouse	6.2
	Flood (2°)	1.8
	"Unwantedness"	2.4
	Maternal depression (3°)	1.8
Obsetric complications (OC)	General class of OCs	2.0
	Hypoxia-related OCs	2.1-4.4
	Perinatal brain damage	7.0
	Low birthweight (<2500g)	1.6
	Pre-eclampsia	2.5

Gene-environment interaction

The effect sizes for these prenatal and perinatal risk factors are small, with odds ratios or relative risks of around two (see Table 2.4). Similarly, the results of genetic studies in the past decade suggest that multiple genes with small effect sizes are involved in causation of schizophrenia (Jones and Murray, 1991, Tsuang, 2000). Taken together these and other findings indicate that we are likely to be dealing with interactive effects of prenatal and genetic factors. The presence of interactive effects has implications for statistical power, model-building and study design.

In thinking about causation, we will increasingly have to take into account the dynamic interplay between genes and environment in utero. While development is genetically programmed, the program is continually modified in utero, as the expression of genes is determined in part – as when genes are turned on or off – by their molecular environment (Kandel, 1998). Furthermore, both epidemiologic and animal studies increasingly support the view that the uterine environment has a profound impact on developmental programming (Barker, 1992; Liu et al, 2000). Thus, normal variation in the fetal environment may have important implications for offspring risk of schizophrenia, because it modifies the developmental program. We do not yet know the relative importance for schizophrenia risk of specific fetal insults such as infection and normal fetal variation such as in fetal nutrient supply.

The interplay between genes and environment may precede even the conception of the offspring at risk for schizophrenia. Recent findings confirm earlier reports that increasing paternal age is associated with an increased risk of schizophrenia (Hare et al, 1979, Malaspina et al, 2001).

Fortunately, techniques for investigating genetic and environmental risk factors are beginning to converge, with case-control and cohort designs being used for genetic association studies. Molecular genetic studies are including measures of environment and cohort studies are collecting both DNA samples and information on early and later environmental risk factors. In the coming decade we may see the first reports of studies that examine precisely measured genetic and environmental causes of schizophrenia in the same population.

Chapter 3

Background: Childhood development and later schizophrenia

3.1 Schizophrenia as a developmental disorder

From its first descriptions, schizophrenic psychosis had a longitudinal dimension (Clouston, 1892; Murray, 1994; Murray & Jones, 1995). Both Kraepelin (1896) and Bleuler (1908; 1911) noted that people who developed the psychotic syndrome were often different from their peers before psychosis began. By the middle of the 20th Century the observation that there may be psychological differences predating psychosis had been incorporated into the psychodynamic formulations prevalent at that time and was not seen to have any biological significance. However during the 1980's, as discussed in the previous chapter, a new causal paradigm emerged: the 'neurodevelopmental hypothesis' of schizophrenia (Murray & Lewis, 1987, Weinberger, 1987).

The existence of neurological or behavioural abnormalities during childhood or adolescence before the onset of overt psychotic symptoms provides crucial support for the neurodevelopmental model. Accordingly, information about childhood development and schizophrenia has been gleaned from a wide variety of sources over the past 4-5 decades including: school records (Watt et al, 1978; Cannon et al, 1999), child guidance clinic records (Robins 1966, Hartman et al, 1984, Ambelas, 1992, Hollis 1995, Cannon et al, 2001), conscript assessment records (Malmberg et al. 1998, David et al.1997, Davidson et al, 1999) and even childhood 'home movies'. (Walker et al. 1990, 1993, 1994). Although many of these samples are biased to varying degrees, as a body of evidence, they point to many social, behavioural, motor and intellectual precursors of schizophrenia (Rutter, 1984, Jones 1999, Marenco and Weinberger, 2000). This chapter will focus on evidence of childhood developmental deficits preceding schizophrenia taken from two robust sources of prospective information: genetic high risk cohorts and general population birth cohorts.

3.2 Evidence from Genetic High Risk Cohorts

In the genetic high-risk design, individuals with a higher than normal genetic loading for schizophrenia, by virtue of having at least one affected first degree relative (usually a parent) are identified and studied longitudinally. Individuals with one schizophrenic parent have a slightly greater than 10% risk of developing schizophrenia – 10-12 times higher than the risk in the general population. This design entails determining whether measures, assessed at one time point, predict later manifestation of schizophrenia and related disorders. These high risk studies permit the opportunity to observe the developmental course of schizophrenia and offer the possibility that characteristics assessed early in life can be used to differentiate offspring who develop psychopathology from those who do not. I will review the major high risk studies from the point of view of gaining information about childhood development in children at genetic risk for schizophrenia and as precursors and predictors of adult schizophrenia. The high-risk studies recruit children at different times in the life span see Table 3.1. Two studies, the Fish High-Risk Study (Fish et al 1992) and the Jerusalem Infant Development Study, (Marcus et al 1981, Marcus et al, 1993, Hans et al, 2000), began follow-up from infancy. Others such as the New York High Risk Project and the Israeli High Risk Study began in early and middle childhood. Studies that began in adolescence, such as the Copenhagen High Risk Study and the Edinburgh High Risk Study are less informative about childhood development. So far only a few high-risk studies have followed subjects from childhood through into adulthood: the high risk study of Barbara Fish (Fish, 1992), the Copenhagen High Risk Study, the Israeli High Risk study (Mirsky, 1995) and the New York High Risk Project (Erlenmeyer-Kimling et al, 2000).

Problems associated with the high risk design include small samples sizes, incomplete follow-up and the perennial problem of generalizability (since only 10% of schizophrenic patients have a parent with a diagnosis of schizophrenia). The issue of generalizability can be examined by comparing the results of the genetic high risk cohorts with general population birth cohorts. The reliance on parental reporting for some behavioural measures may be problematic in samples selected for parental pathology. It is unclear for many of the studies whether offspring were examined blind to high risk status. The Fish High Risk study has been criticised because neither the childhood assessments nor the adult outcome assessments were made blind to group status.

Table 3.1 Genetic high risk studies of schizophrenia (reviewed in this chapter)

High Risk Study	Age at recruitment	Age at last assessment	Complete 'C'or Ongoing 'O'
New York Infant Development Study (Fish)	Birth	27-34 years	C
Jerusalem Infant Development Study	Birth	14-21 years	O
Copenhagen Obstetric High Risk Study	Birth	1 year	C
New York High Risk Project	Mean 9 years	Mean 30 yrs	O
Israeli High Risk Project	Mean 11 years	35-36 years	C
Copenhagen High Risk Study	Mean 15 years	Mean 42 yrs	C
Finnish Adoptive Study of Schizophrenia	Mean 16 years	21-23 years	O
Edinburgh High Risk Study	Mean 21 years	Mean 24 yrs	O

What do we need to know about childhood developmental markers of schizophrenia from genetic high risk studies?

- Which childhood developmental impairments are associated with genetic risk for schizophrenia?
- Which childhood developmental impairments predict later schizophrenia among those at genetic risk?
- What is the nature of the relationship: subgroup, dose-response or other ?
- What about the false positives – ie those with childhood developmental impairments who do not develop schizophrenia? Can they provide us with information about interactive risk factors or protective factors?
- Are the findings from high-risk studies regarding childhood development generalisable to the majority of schizophrenia?

3.2.1 Studies with information from infancy

New York Infant Development Study

Barbara Fish began the New York Infant Development Study in 1952 and identified at birth 12 offspring of chronic schizophrenic mothers and 12 controls from similar low SES backgrounds. Developmental assessments were made at 10 points between birth and age 2 years. Subsequent assessments were carried out at 9-10, 15-16, 18-19 and 20-22. The last assessment of current psychiatric status to date was at 1991, when the cohort were aged between 27-34 years. From her detailed infant observations, Fish noted *abnormal timing and pattern of acquisition of milestones and growth retardation* among the high-risk group (Fish, 1959, 1973). She invented the term *'pandysmaturation'* (PDM) to describe this constellation of infant developmental abnormalities (Fish, 1987). She considered PDM to be a marker in infancy for an inherited neurointegrative defect in schizophrenia, as in Meehl's 'schizotaxia' hypothesis (Meehl, 1962, 1989). Of the seven high risk children diagnosed with PDM, all have been subsequently diagnosed (non-blindly) with schizophrenia or schizotypal personality disorder in adulthood (Fish, 1987). Fish partially replicated her findings in the Jerusalem Infant Development Study (see below) and concluded that PDM may provide a strategy for identifying at-risk individuals before adult psychopathology becomes evident (Fish et al (1992).

The Jerusalem Infant Development Study

The Jerusalem Infant Development Study (JIDS) recruited high risk and control children at birth (1973/77), and detailed information is therefore available from infancy on the subjects. The sample sizes vary at each assessment as siblings have been recruited to increase the numbers in the offspring groups. At the latest follow-up assessment, the sample comprised 24 offspring of schizophrenic parents; 25 offspring of parents with other mental illness, and 16 offspring of parents with no mental illness. However the subjects have not yet reached the peak risk period for schizophrenia so one cannot yet identify predictors of later schizophrenia with any degree of certainty. The subjects have been followed up at school age (7-13 years) (Marcus et al, 1993) and in adolescence (14-21 years) (Hans et al, 1999).

A global measure of poor neurobehavioural functioning was derived from factor analysis of 20 neurobehavioural variables. This resulted in 2 principal components: cognitive–attentional and

motoric. The sample was divided into good and poor functioning by an Epanechnikov kernel procedure. The offspring of schizophrenic parents were three times more likely to be thus defined as poorly functioning when compared with offspring of non-schizophrenic parents (Hans et al, 1999) - 40% of offspring of schizophrenic parents showed consistently poor functioning at all 3 assessments. Although the JIDS offspring are still early in the period of risk for schizophrenia, 7 subjects have already received diagnoses in the schizophrenia spectrum. Four are offspring of schizophrenic parents (1 schizophrenia, 1 schizotypal personality disorder and 2 paranoid personality disorder), all of whom showed a consistently poor pattern of neurobehavioural functioning at both school age and adolescence, and 3 out of 4 also showed poor infant functioning and probable PDM (Fish et al, 1992). These findings from the current assessment of the JIDS support the hypothesis that global neurodevelopmental deficits detectable from early infancy may be premorbid indicators of genetic vulnerability to schizophrenia.

Obstetric Copenhagen High Risk Project

This project differs from the others in that it involves record linkage rather than tracing or interviewing subjects (Mednick et al, 1971). A perinatal register from the University Hospital in Copenhagen containing information on obstetric histories and 1-year developmental checks on children born between 1959 and 1961 was linked with the Danish Central Psychiatric Register. The sample for this study comprised 83 children born to a schizophrenic parent, 83 children born to a parent with personality disorder and 83 children born to normal parents. Retarded motor reflexes in the neonatal period and retarded one-year development among the schizophrenia offspring (late in attaining milestones) were observed among the high risk schizophrenia group. Low birth weight was significantly related to one year developmental status among the offspring of schizophrenic parents only. This ingenious high-risk study provided further evidence that early developmental impairments are makers of genetic risk for schizophrenia.

3.2.2 Studies with information from Middle Childhood

Israeli High Risk Study

The Israeli High Risk study began in 1964 with the aim of capitalizing on a unique child-rearing circumstance found nowhere else in the world – the children's house in the kibbutz. A professional child care worker or *metapelet*, is responsible for rearing the children in a communal children's house, although the children usually spend some part of the day with their parents. The study aimed to identify a group of children at genetic risk for schizophrenia who were being raised on kibbutzim and to follow them over time. It was postulated that the stability and continuity afforded the group-raised children would have a favourable effect on their development, as such children would be less likely than those raised in the nuclear family to suffer the unpredictable behaviour and frequent absences of a mentally ill parent (Mirsky, 1995).

Fifty index children at high risk for schizophrenia (offspring high risk) and 50 control children were identified at mean age 11. They were assessed again on three occasions: at mean ages 17, 26 and 36 years respectively. The initial data from the first and second round of interviews provided numerous instances of the ways in which index children differed from controls (Marcus et al, 1985). The differences involved virtually every area of functioning and included soft neurological signs such as clumsiness, poor left-right orientation, impaired visual motor co-ordination and greater distractibility; lower sociometric rankings by peers and impaired interpersonal relations, work and play activities, self esteem and mood.

Circumstances of rearing and later psychopathology

In order to examine the effects of kibbutz vs nuclear family rearing the sample was recruited so that the 50 high risk (index) and 50 control children could be subdivided into equal groups of 25 as follows: the kibbutz index (KI) group and the town index (TI) group, the kibbutz control (KC) group, and the town control (TC) group. However the reason for children being assigned to kibbutz or home upbringing was not known. At follow up when aged 26 (Mirsky et al, 1985), the KI group (23 interviewed) had the highest incidence of psychiatric disorder comprising: 3 schizophrenia and 3 other schizophrenia spectrum, 5 major affective, 4 minor affective, 1 other diagnosis, 7 no diagnosis Corresponding figures for the 23 members of the TI group interviewed were: 2

schizophrenia, 1 other schizophrenia spectrum, 1 major affective, 0 minor affective, 3 other diagnosis, 16 no diagnosis. There were a total of 4 minor diagnoses for the control groups and 40 control cases with no diagnosis.

At the last follow up no new cases of schizophrenia were found (Mirsky , 1995). However 44% of the KI group had a severe Axis 1 disorder compared with 16% in the TI group (p=0.03). Only 8% of the pooled control group (KC + TC) had an Axis 1 disorder (p=0.0007). The authors concluded that kibbutz rearing in high risk children significantly increases their risk of major psychiatric disorder– though not necessarily schizophrenia. What are the potential mechanisms for this effect? One possibility is that conformity to kibbutz norms is greatly encouraged and deviant or odd behaviours are not tolerated, therefore differences between children vulnerable to schizophrenia and controls would be exaggerated in the 'hot house' atmosphere of the kibbutz and would add to their feelings of isolation and loneliness. Another stress for the kibbutzim-reared child lies in the forced conformity and intolerance for deviation involved in the mandatory military experience.

Other childhood predictors of later schizophrenia

The social and behavioural profile (at 11 and 17) of the index child who developed schizophrenia spectrum disorder was as follows: antisocial person, did not get on with parents, teachers or peers, was rated low in social desirability by peers, low self-esteem, suspicious and withdrawn, and had poor communication skills. (Hans, et al, 1992). Poor attention skills at age 11 were highly related to development of schizophrenia spectrum disorders in adulthood (Mirksy, 1995).

Protective factors

Index cases who were free of any diagnosis at the last follow-up had the highest 'sense of coherence' scores of any group, suggesting that positive self esteem may be a protective factor for subjects at risk of schizophrenia (Mirsky, 1995). The future affective disorder cases had the highest IQ of all subjects (Mirsky, 1995). Higher IQ may also serve as a protective factor among high risk children in that affective disorder rather than schizophrenia developed.

The New York High Risk Project

The New York High Risk Project (NYHRP), Erlenmeyer-Kimling et al (1995,1997) began recruiting subjects in 1971/71 (Sample A) with a second round of recruitment in 1977-79 (Sample B). Children were recruited at ages 7-12 years (mean 9.5 yrs). The samples comprised 79 offspring of schizophrenic parents, 57 offspring of parents with affective disorder (40% were psychotic) and 133 offspring of parents with no mental illness. There has been some reclassification of parents originally diagnosed as schizophrenic as suffering from affective illness. Children have been assessed at 6 evaluation rounds, about 3 years apart between ages 7-12 and ages 26-30 years. The last assessment was in 1994/1995 (mean age 30.1 years) when full diagnostic assessments were carried out. At that time 15% (n=12) of the 79 offspring of schizophrenic parents, 7% (n=4) of the 57 offspring of the affectively-ill parents and 0.8% (n=1) of the 133 offspring of normal parents fulfilled diagnostic criteria for schizophrenia-related psychoses (Erlenmeyer-Kimling et al, 1995, 1997).

Neuropsychological predictors of later schizophreniform disorder

At the baseline assessment at age 7-12 a neuropsychological battery was administered to the children (Erlenmeyer-Kimling et al, 2000). Poor performance in test of attention, memory and gross motor skills were significantly related both to high-risk status and to risk of later developing a schizophreniform psychosis among the high-risk group.

Combination of impairment on all three variables together achieved better classification among the offspring of schizophrenic parents with respect to false positive rate, positive value and overall accuracy than any of the variables individually (Erlenmeyer-Kimling et al, 2000). For a model containing all three variables, sensitivity in identifying the future development of schizophrenia-related psychoses among offspring of schizophrenic parents was 50%, with a specificity of 89.6%, positive predictive value of 46.2% and overall accuracy of 83.5%. The false positive rate was 10.4%. The nonpsychotic offspring of schizophrenic parents who were among the 10% falsely classified when all three variables were combined are of interest because they appear to be carriers of some of the susceptibility genes for schizophrenia and may yield information about some of the other factors that may be needed for the development of overt

illness. It is of course possible that some of these 'false positive' subjects will express the clinical illness in the future. Among the offspring of affectively ill parents, no subjects were predicted to develop schizophrenia-related psychosis by all three models. Alternatively, false positive subjects may have experienced less exposure to environmental factors that interact with susceptibility genes for full clinical expression of the illness.

It is likely that deficits in attention, memory and gross motor skills reflect only some of the phenotypic indicators of a large complex of susceptibility genes, as there remains a significant effect of family background on schizophrenia-related psychoses when the influence of these three mediating variables is controlled. Other measures such as functional brain imaging, or more refined neuropsychological batteries may have been better predictors. Impaired attention in childhood has been noted as a stable trait through childhood and into adulthood in those at risk of schizophrenia in the NYHRP, (Cornblatt et al 1985, 1994, Erlenmeyer – Kimbling et al 1992).

Behavioural predictors of later schizophrenia

Childhood behavioural problems in the NYHRP were rated from a parent interview at the first assessment when the children were aged 7-12 years, (Amminger et al, 1999). A childhood behaviour measure was derived from this interview using factor analysis. The resulting childhood behaviour variable reflected mainly externalizing behaviours. Items reflecting other behaviours such as social withdrawal did not yield sufficiently high loadings to be included in the behaviour item used in the analysis. No differences between the offspring groups (high-risk schizophrenia, high-risk affective and control) were found with regard to childhood behaviour, but after exclusion of subjects who later developed substance abuse, subjects who developed adulthood schizophrenia-related psychoses (from Sample A) displayed significantly more behavioural problems in childhood than those with adulthood affective disorders or anxiety disorders or those with substance abuse only or no disorder.

Cognitive predictors of later schizophrenia

Intelligence scores, (on WISC and WAIS), were lower in the offspring of schizophrenia parents than the offspring of affective disorder parents at the first assessment (mean age 9.4 years) but not at the second assessment (mean age 15.2 years) (Ott et al, 1998). Overall IQ as measured in adulthood could not be conclusively linked with later schizophrenia. However a low score on the

measure of scatter (the variability in performance between subtests at the individual level) was a significant predictor of later schizophrenia-related psychoses. The authors speculate that low levels of scatter indicate a flattening of the cognitive profile in the pre-schizophrenic state, possibly related to inflexibility of cognitive functioning, but without deficiencies of particular abilities.

3.2.3 Studies with information from adolescence

Copenhagen High Risk Study

The Copenhagen High Risk Study is the largest high risk study in schizophrenia conducted to date and began in 1962 by recruiting 207 offspring of schizophrenic mothers and 104 offspring of control mothers when the children were on average 15 years. The study is also notable in that it followed subjects right through the risk period for schizophrenia – up to 42 years of age on average. At the last assessment (Mednick et al, 1987) 19% of the high risk offspring fulfilled diagnostic criteria for an Axis 1 functional psychotic illness, 20% fulfilled diagnostic criteria for Cluster A personality disorder and a further 20% fulfilled diagnostic criteria for other Axis 1 and 11 disorders. Among the low risk offspring only 2.8% fulfilled diagnostic criteria for an Axis 1 functional psychotic illness, 5.5% filled diagnostic criteria for Cluster A personality disorder, and 32% fulfilled diagnostic criteria for other Axis 1 and 11 disorders.

Although the recruitment in the mid teens means that there were no assessments of the sample in childhood nevertheless some childhood data is available from obstetric records and from teacher reports. Mednick et al (1987) reported that high risk subjects who later developed schizophrenia had experienced more and more severe perinatal complications than those who did not. Teacher reports were available for this sample at age 15 (Olin and Mednick, 1996). Teachers more frequently

judged children later diagnosed with schizophrenia to be emotionally labile and more susceptible to future breakdown with some gender differences: males were rated as disruptive, disciplinary problems, anxious, lonely and rejected by peers and more likely to have repeated a grade, while females were rated as nervous and withdrawn. In a reanalysis of this project, Cannon et al (1990)

separated predominantly negative symptom schizophrenia from predominantly positive symptom schizophrenia. The former were rated by teachers to be passive, socially isolated and unresponsive to praise, while the latter were rated as overactive, irritable, distractible and aggressive.

Finnish Adoptive Family Study of Schizophrenia

The Finnish Adoptive Study of Schizophrenia focuses on family environment as a risk factor for later schizophrenia (Tienari et al, 1987). It is not informative about childhood development but has given interesting information on gene-environment interaction in schizophrenia.

A nationwide sample was collected of all women who had been hospitalized because of schizophrenia, between 1960 and 1979 in Finland (n=19,447). Through linkage with adoption registers it was found that 264 of these schizophrenic mothers had given up 291 offspring for adoption. A total of 179 adopted-away offspring of 164 index schizophrenic mothers comprised the final sample of index cases. Subjects were recruited at a mean age of 16 years. Index cases have been matched with control adoptees and their adoptive families. The adoptive index and control families have been intensively studied in their homes with 2-day assessments, including couple and family interviews, the consensual Rorshach and the interpersonal perception method. Follow-up telephone interviews 5-7 years after the original assessment, revealed that 15 adoptees have developed a psychotic illness: 13 from the index group and 2 from the control group. The families were divided into two groups on the basis of their globally-rated family functioning: healthy, and disturbed (moderately/severely). In the healthy rearing families there was little mental illness among the adoptees regardless of whether or not the biologic parent was schizophrenic. In disturbed families the adoptees are much more disturbed, especially among the index adoptees (Tienari, 1991). The results are consistent with the hypothesis that healthy families have possibly protected the vulnerable child from developing schizophrenia, whereas in disturbed homes the vulnerable children are more sensitive to dysfunctional rearing.

An extension of the evidence for gene-environment interaction involved a narrower measure of family pathology – communication deviance – than the original global rating, and a measure of thought disorder as an indicator of vulnerability to schizophrenic illness (Wahlberg et al, 1997). This analysis also addresses the issue of reverse causality (ie whether a disordered child can alter the family dynamics or communication style of the parents. In a subsample of 58 index and 96

comparison adoptees and their families, there was no significant relationship between index or control status of the adoptee and communication problems in the rearing parents. There was a highly significant gene-environment interaction effect. In the families with high levels of communication deviance, a higher proportion of high-risk than comparison adoptees showed evidence of thought disorder. This is an example of genetic control of sensitivity to the environment, the extent to which genes control the degree to which individuals are sensitive to the predisposing, risk-increasing aspects of the environment.

The Edinburgh High Risk Study

This study has recruited subjects with at least two family members with a diagnosis of schizophrenia (Hodges et al, 1999, Johnstone et al, 2000). High risk subjects were recruited from age 16-25 years and this study is therefore not informative about early childhood development. The focus is on identifying neuroimaging and neuropsychological predictors of genetic vulnerability to schizophrenia. The high risk group report more psychiatric contacts during childhood and adolescence, more childhood antisocial behaviour, childhood social isolation and interpersonal sensitivity than normal controls (Hodges et al, 1999). Significant neuropsychological differences between high risk subjects and controls at baseline were observed for all tests of intellectual function and on aspects of executive function and memory (Byrne et al, 1999).

3.2.4 Summary of the data on childhood development from the high – risk studies

- Genetic high risk studies of schizophrenia show that between 25-60% of high risk children display some or all of the following developmental abnormalities: pandysmaturation (infancy), gross and fine motor impairment (early childhood), attentional and information processing deficits (early and middle childhood), cognitive and neuropsychological deficits (childhood and adolescence), and behavioural problems and social adjustment difficulties (adolescence). These deficits may indicate the influence of susceptibility genes for schizophrenia

- Motor, memory and attentional deficits are predictive of later schizophrenia-related disorders among high risk children, with positive predictive values of about 50%.

- The circumstance of the child's upbringing (deviant communication within the family or kibbutz-rearing) appears to interact with genetic risk for schizophrenia and may increase the risk of subsequent schizophrenia and other major psychopathology.

- The false positives: the high risk children who have developmental impairments but do not develop schizophrenia are interesting because they could provide information about possible protective factors or other risk factors required to precipitate the onset of schizophrenia. However the high-risk samples have not yet been followed through the entire period of risk. More information about false positives can be obtained in the following section under discussion of the National Collaborative Perinatal Project.

3.3 Evidence from General Population Birth Cohort Studies.

General population birth cohorts provide a valuable source of unbiased and prospective data on childhood development that is not restricted to patients with an affected first degree relative. A wide range of factors can be examined within one study, confounding can be controlled and causal pathways can be explored. These cohorts are derived from a general population of births and are unselected for specific genetic or environmental exposures. The cohort usually undergoes a comprehensive assessment at birth or during early childhood and at subsequent follow-ups. Data on child development is usually detailed and standardized. The recent prominence of these types of studies in the psychiatric literature is due to the 'coming-of-age' of birth cohorts that were established by far-sighted researchers many decades earlier (Susser, 1999). Outcome data is usually obtained through psychiatric screening interviews in adulthood or linkage to national health care registers. The major problem with these cohorts, as discussed in Chapter 1, is the difficulty obtaining sufficient cases for analysis, stemming from the relative rarity of schizophrenia in the general population. One approach to overcoming this problem is to use nested case-control designs (Cannon et al, 1999), or to combine data from several similar cohorts (Jones and Done, 1997; Susser, 1999).

Medical Research Council National Survey of Health and Development (NSHD)

Jones and colleagues (1994,97), reported on the Medical Research Council National Survey of Health and Development. This cohort is a stratified, random sample of births occurring in Britain during a week in March 1946 (Wadsworth 1991). In this survey, 5362 children were followed up at regular intervals, including 11 contacts up to the age of 16 years. Since that time there have been 9 contacts, with the most recent at 43 years. Cases of schizophrenia were identified on the basis of information from the cohort questionnaires, the Present State Examination at age 36, and the Mental Health Enquiry, a central independent register of psychiatric hospital admissions. Of 4,746 subjects alive and living in the United Kingdom at age 16, 30 subsequently met the DSM-III-R criteria for schizophrenia. The remaining 4,716 subjects were considered to have been at risk and were used as control subjects.

The children who later developed schizophrenia were shown to have a significant delay in achieving developmental milestones over the first two years of life. At age 2 they were less likely

to have attained all the milestones of sitting, standing, walking and talking. Walking and talking showed the greatest differences with the cases having an average delay of 1.2 months for each. Between ages 2-15 speech problems were also more frequent.

Consistently poorer results in the cognitive tests, conducted at ages 8, 11 and 15, were achieved by the cases when compared with the controls. Particular areas of deficit were verbal, non-verbal and mathematical skills. These differences appeared to widen in adolescence although this was not statistically significant. In terms of sociability, the children who later developed schizophrenia preferred to play on their own at ages 4 and 6, and showed a statistically significant linear trend for being more socially anxious as teenagers. There was no indication that low social class or disadvantaged home circumstances was associated with the later development of schizophrenia.

Regarding specificity of these precursors to schizophrenia and affective disorder, van Os et al (1997) used the same birth cohort to show that female gender and lower scores on childhood cognitive tests predicted later depression in the total group of subjects. For those who developed childhood-onset affective disorder there were also significant discriminant characteristics in later motor milestones attainment and the presence of more twitches and grimaces at the age of 15. Those in the adult onset affective disorder group only did not show these developmental delays and abnormal movements.

The National Child Development Study (NCDS)

Another British birth cohort with a similar design and findings with regard to schizophrenia has been reported on by Done et al (1991, 1994) and Crow et al, (1995). The National Child Development Study (NCDS) followed subjects born in a week in March 1958. Data were collected at birth and at ages 7, 11, 16 and 23 years. At age 7, 15,398 subjects were traced. Cases were identified by means of the Mental Health Enquiry (see previous section) and Present State examination diagnoses were made from ratings of medical notes. By 1994, 29 of the subjects were judged to have a 'narrow' diagnosis of schizophrenia, 29 were considered to have undergone an affective psychosis and 71 were judged to have a (hospital-treated) neurotic illness. A control group comprised a randomly selected sample (10%) of cohort members who had not received psychiatric treatment.

Ratings of motor function and neurological soft signs were made at ages 7 and 11. At age 7 the cases that went on to develop narrowly defined schizophrenia and affective psychoses were significantly more abnormal than controls on coordination and clumsiness (Crow et al, 1995). At age 11 differences in hand preference, relative hand skill, coordination and CNS impairment were apparent for the schizophrenia group compared with controls.

Poorer educational achievement was found in the group who went on to develop schizophrenia. This encompassed a wide range of tasks and there was no change in the relative difference between the cases and controls over the age range 7 to 16 (Crow et al, 1995). Only minor cognitive deficits were measured for the pre-affective psychosis subjects. A combined analysis of the 1946 and 1958 cohorts (Jones and Done, 1997) shows that the lower the IQ at age 11 years the greater the risk for schizophrenia – a population shift of 0.4 standard deviations (95% CI 0.05-0.75). Inspection of the frequency distributions of IQ for the samples combined reveals no evidence of a subgroup, the overall impression is of a general shift of the distribution. There was no evidence of a threshold effect.

1966 Northern Finland Birth Cohort

This cohort was started in 1966 and prospectively followed 12 058 children live born in that year (Isohanni et al 2000). Data have been collected up until age 31 on 11 017 members of the cohort who were living in Finland at the age of 16. Later achievement of developmental milestones, (standing, walking or becoming potty trained), in the first year predicted the highest risk of future psychoses, while earlier attainment of these skills held a lower risk than expected. The relationship between age at acquiring motor milestones and risk of psychoses later in life appeared linear (Isohanni et al 1998a, 2001 submitted). Adolescents who performed at school below their expected grade were 3 times more likely to develop schizophrenia than those in their normal grade (Isohanni et al 1998b). However, a small sub group of boys who had a 4 fold increased risk of developing schizophrenia compared with comparison subjects had excellent school performance (Isohanni et al 1999). Hence both poor and excellent performers scholastically in this cohort appear to have an increased risk of schizophrenia.

Swedish Conscript Cohort

This Swedish cohort consisted of 50,087 young men aged 18 years who were assessed for conscription into the Swedish army during the period 1969-70. Extensive psychological and personality testing was performed as part of the assessment. Using record linkage to the Swedish Hospital Discharge Register, 195 (0.4%) of this cohort were identified as having been discharged from a psychiatric hospital between 18 and 25 with an ICD-8 diagnosis of schizophrenia (Lewis et al, 1992). Strong linear relationships were found between lower IQ scores measured at age 18 and later development of schizophrenia (David et al, 1997). Since all individuals who had a learning disability, a major neurological condition or an onset of schizophrenia before age 18 were excluded, the strength of these associations may even be underestimated.

Similar strong linear relationships were found between premorbid lack of sociability and sensitivity and increased risk of schizophrenia (Malmberg et al 1998). Subjects with few friends, without a steady girlfriend, who preferred to socialise in small groups and felt more sensitive than other people were more than thirty times more likely to develop schizophrenia than were men with none of these characteristics. Accumulation of exposure to these four variables was associated with a linear increase in the risk of developing schizophrenia – a dose response relationship. A further analysis from the cohort has shown that a diagnosis of non-psychotic psychiatric disorder at age 18 was associated with an increased risk of subsequent schizophrenia (Lewis et al, 2000). In particular those who received a diagnosis of personality disorder at age 18 years had more than twice the risk of developing schizophrenia before age 31. Diagnoses of neurosis or substance abuse at age 18 may reflect prodromal symptoms of schizophrenia.

Israeli Draft Board Conscript Cohort

The Israeli Draft Board assesses all Israeli males at 16 or 17 for their eligibility to military service. Data from these assessments on male adolescents between 1985 and 1991 has been used and linked with the National Psychiatric Hospitalisation Case Registry between 1970 and 1995 to detect cases with schizophrenia, (Davidson et al, 1999). Compared with matched controls healthy males at draft assessment who went on to develop schizophrenia had significantly lower scores on all measures. A linear association between increasing risk for schizophrenia and poorer

cognitive performance was found. A poorer ability to function independently, fewer social relationships
and decreased organizational ability were behavioural characteristics significantly associated with cases compared with controls.

The National Collaborative Perinatal Project (NCPP) – Philadelphia cohort

From 1959 to 1966, the NCPP enrolled for study 9,236 offspring of 6,753 mothers who delivered at two inner city hospital obstetric wards in Philadelphia. In 1996, a search of the Penn Longitudinal Database showed that 3.7% of the cohort members had ever had a psychotic illness (194 with schizophrenia or schizoaffective disorder and 145 with affective or drug induced psychosis), and 9.3% had ever had a non-psychotic diagnosis. A chart review of 144 cases showed that 72 fulfilled criteria for DSM-IV schizophrenia of schizoaffective disorder. This cohort study is unique in that it also allows investigation of childhood development among the siblings of schizophrenic patients: 72 cases had 63 unaffected siblings who were also NCPP study participants.

Siblings of schizophrenic patients are a group at genetic high risk for schizophrenia who have not developed the condition. In a sense they can be viewed as 'false positives', a proportion of the siblings may display the same endophenotypic traits as the probands but have escaped developing the condition. They can be used to study possible markers of genetic liability to schizophrenia that are distinct from the precursors of the condition itself. The sibling design can also allow examination of possible interactive risk factors or protective factors for schizophrenia.

Childhood developmental variables as predictors of schizophrenia or sibling status in the NCPP Philadelphia cohort.

Children were assessed on a number of developmental domains in infancy and again at 4 and 8 years respectively. Variables that were significantly associated with both later schizophrenia outcome and sibling status were:

Motor variables (Rosso et al, 2000b): Poor performance on motor co-ordination at age7 (12.5% of siblings but only 4% of controls were deviant on tests of motor co-ordination). Unusual movements at age 4 and 7 predicted schizophrenia outcome but not sibling status.

Cognitive functioning (Cannon et al, 2000b): Cognitive variables: Both subjects with schizophrenia and siblings performed worse than controls on IQ tests at both 4 and 7 years. There appeared to be an inverse linear relationship between low IQ and risk of later schizophrenia or sibling status.

Language abnormalities (Bearden et al, 2000): Both schizophrenia subjects and siblings performed more poorly than controls on tests of expressive language ability and word association at age 7. Abnormal speech (lack of intelligibility) at age 7 was a highly significant predictor of schizophrenia outcome only.

Behavioural deviance (Bearden et al, 2000): The presence of focal deviant behaviour (such as meaningless laughter or hand motions, excessive crying, echolalia, stereotyped behaviour, speech difficulties, thumb-sucking, nail biting) at both ages 4 and 7 was a significant predictor of both schizophrenia and sibling status. Social maladjustment at age 7 was a significant predictor of schizophrenia only.

The role of obstetric complications:

The role of obstetric complications (OCs) in the development of both childhood handicaps and adult schizophrenia (see chapter 2) raises the question of their contribution to childhood developmental precursors of schizophrenia. Detailed data on OCs was available on the NCPP. The relationship between developmental deficits and later schizophrenia was adjusted for the presence of OCs. Unusual movements at age 4 were associated with hypoxia –related OCs among schizophrenic patients. However apart from this, there were no significant relationships between OCs and any of the other developmental variables among the schizophrenic group. The results suggest that childhood developmental impairments in schizophrenia may represent relatively stable indicators of genetic etiologic influences.

3.3.1 Summary of information on developmental markers in schizophrenia from birth cohort studies

- There is strong and consistent evidence of delays in attaining developmental milestones, cognitive and language deficits and abnormalities in social functioning in childhood among individuals who go on to develop schizophrenia or schizophreniform disorder in adulthood.
- These developmental effects can be noted from infancy and persist throughout childhood, adolescence and early adulthood, providing support for life span models of schizophrenia.
- The relationship between developmental impairments and later schizophrenia appears to be linear – a dose-response relationship, with little evidence for a 'developmental' subgroup.
- Both genetic high-risk and birth cohort studies show remarkable confluence of results suggesting that results of the former are relevant to the majority of cases of schizophrenia.
- These developmental deficits do not appear to be mediated by obstetric factors and their presence in siblings supports a genetic aetiology.
- However specificity of these developmental deficits for schizophrenia has not been established and the statistical power of individual cohorts to examine effects has been low due to small numbers of schizophrenia cases.

Chapter 4

An investigation of school performance and obstetric complications as risk factors for later schizophrenia in a population-based study in Helsinki, Finland.

4.1 Introduction

I have outlined in previous chapters (Chapters 2 and 3) that differences in development and behaviour have been found among children who later develop schizophrenia, as far back as prenatal and perinatal life. As discussed in Chapter 1, longitudinal developmental research relies heavily on prospective cohort studies, but this design is not entirely suitable for schizophrenia research because of the low incidence of the illness and the long follow-up period required. One solution is to use cohorts that were set up for other reasons. This 'opportunistic' stategy has already produced important results, but the major disadvantage is that it yields relatively few cases of schizophrenia with consequent low statistical power. The 'nested' case-control design includes all cases within a cohort but only a selection of comparison subjects, and is efficient of resources while combining the advantages of both cohort and case-control studies, (Rothman and Greenland, 1998; Langholtz and Thomas, 1990). The study outlined in this chapter uses a nested case-control design to examine prenatal, perinatal and childhood risk factors for schizophrenia. This design affords many advantages: the general population base minimises selection bias, the standardised prospectively-recorded childhood data minimizes information and recall bias, and the large number of cases gives high statistical power to examine effects.

4.1.1 Aims and hypotheses

The aims of this study were:

(1) To examine the school performance of children who would later develop schizophrenia compared with their peers. The specific hypotheses, informed by the previous literature review were:

1. That children who would later develop schizophrenia would perform more poorly in school than their peers, particularly on academic subjects
2. That children who would later develop schizophrenia would exhibit more behavioural problems in school than their peers.

(2) Secondly, this study aimed to examine obstetric complications as risk factors for schizophrenia. The specific hypotheses were that:

1. Children who later developed schizophrenia would have a greater number of hypoxia-related complications than controls
2. Children who later developed schizophrenia would have lower birth weight than controls.
3. Children who later developed schizophrenia would have more pregnancy-related complications than controls.

4.2 Study population

The study population comprised all individuals who were born in Helsinki, Finland between 1951 and 1960. Cases of schizophrenia born during this ten-year period were ascertained from three national computerised databases: the Finnish Hospital Discharge Register, (FHDR), and two registers of the Social Insurance Institution: the Pension Register and the Free Medicine Register. The data in all registers were linked using the unique social security number for each individual. Information from these registers was available for the period 1969- 1991. Before 1987, the ICD-8 (WHO, 1969) diagnostic system was used, after which diagnoses were coded according to ICD-9, (WHO, 1977) using DSM-III-R criteria (APA, 1987). Details of these diagnostic systems and a discussion of the 'narrow' Finnish diagnostic practices have been provided in Chapter 1. The Social Insurance Institution indexes only the first three digits of diagnostic codes. Therefore all individuals with a '295' diagnosis according to ICD-8 and ICD-

9 numbering schemes were defined as cases; this included individuals with schizophrenia. schizoaffective disorder or schizophreniform disorder. The FHDR covers all public and private hospitals in Finland and the discharge diagnoses for each admission are made by the attending physician. The Free medicine register and the Pension register give primary diagnoses for individuals receiving state-subsidised outpatient medication and disability pensions, respectively. All Finnish citizens have free access to inpatient and outpatient health care and are entitled to a state-funded disability pension, and more than 90% of psychotic patients in Finland come into contact with the health care system in at least one of those ways (Lehtinen et al, 1990, Lehtinen et al, 1991). The diagnostic validity of the FHDR has been examined against DSM-III-R criteria and has been found to have excellent, (92-100%), specificity for diagnoses of schizophrenia (Isohanni et al, 1997). In total 928 individuals were identified from the registers who had received a '295' diagnosis, and who were born in Helsinki between 1951 and 1960.

Information on correlates of illness

The FHDR provided information on age at first admission and duration of hospitalization. Onset was considered to be the age at first diagnosis with schizophrenia. Nineteen cases (4.7%) had onset of illness at or below 18 years of age. The main analyses were conducted with and without these cases, and since the results were not significantly different, these early-onset cases are retained in subsequent analyses.

Familial loading score

Record linkage between the health care registers and the National Population Register gave data on psychiatric diagnoses in first-degree relatives. A familial loading score was calculated for each case to estimate genetic risk for schizophrenia (Verdoux et al, 1996). This score, which takes account of family size and age structure, was based on the following assumptions: the lifetime risk of schizophrenia in a first-degree relative is 10% for familial probands and 0.5% for sporadic probands; and the age range at risk is 15 to 50 years, with a linear increase in risk from zero to lifetime risk. The likelihood ratio of a proband being familial or sporadic, given that a relative of age x is affected is $[(0.1)(x-15)/(50-15)]/[(0.005)(x-15)/(50-15)]=20$, and the likelihood ratio if a relative of age x is unaffected is one minus this. Such a likelihood ratio was calculated for each relative, and an overall likelihood ratio for whether the proband was familial

or sporadic was obtained by multiplying together the individual likelihood ratios. The loading score was obtained by taking the logarithm of the product. A loading score of zero indicates equal support for the proband to be familial or sporadic. A positive score indicates greater support for familiality, while a negative score indicates greater support for the proband to be sporadic. This loading score has been used previously on a Finnish register- based sample (Suvisaari et al, 1998).

Selection of controls

Controls were identified from the Child Health Clinic Archives of Helsinki City. These Child Health Cards give information on child health checks carried out on children living in Helsinki city between infancy and school age. The record cards are stored in alphabetical order by year of birth. Child health cards were located for 486 of the cases (52%) in the city archives. The next Helsinki-born child with a different surname listed after each case in the Child Health Clinic archives was taken as a control. If the next card also belonged to a case, the previous card was taken as the control. All individuals with '295' diagnoses were included among our cases, but other psychiatric diagnoses were not excluded from the control group. In total, 486 controls were identified by this method. The names of all schools attended by cases and controls were entered into a database. Paternal occupation was also noted. In addition, the name, date of birth, mother's name and date of birth or age (if available) were noted for controls. Child Health Cards in Helsinki City were obtained for only 52% of the cases listed on the register. The main reasons for this attrition were two-fold. Firstly, the two main obstetric hospitals are based in Helsinki city and women may have come from outlying areas to give birth there but were not actually living in Helsinki City at the time. Secondly, during the 1960's and 1970's there was a large expansion of the suburban areas around Helsinki and families with young children, from all social groups, moved out of the city at that time.

Socio-economic group

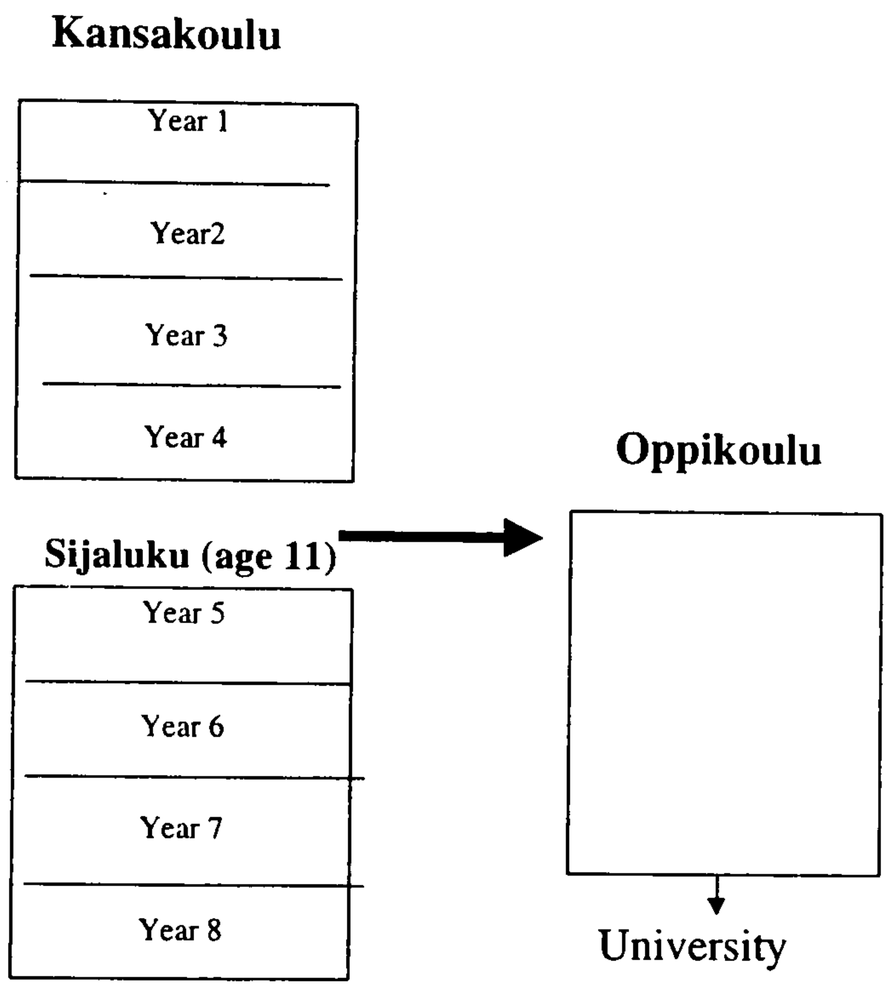
Paternal occupation was recorded on the Child Health Cards. Four socioeconomic groups were identified based on the City of Helsinki Social Group Classification (Tilastollinen päätoimisto, 1971): [22] (1) professionals, managers and higher administrative or clerical employees, (2) lower clerical employees, (3) skilled workers, (4) unskilled workers. In the analysis these were collapsed into two groups: professional/clerical and skilled/unskilled workers.

4.3 Investigation of school performance measures as risk factors for schizophrenia

4.3.1 Introduction

The Finnish elementary school system

Fig. 4.1 Elementary school system in Finland during 1950s/60s



During the period of this study, children in Finland attended an elementary school (kansakoulu) from the age of 7 years (Helsingin kaupungin suomenkieliset kansakoulut, 1955, 1966). The elementary school system is illustrated in Figure 4.1.

Children attended the school that was closest to their home. Children who did not attend the state educational system included: severely deaf children, blind children, severely brain-damaged children, and some children in institutional care. Children who were educationally retarded (1.3-1.9%) or who suffered from emotional or conduct disorder (0.3-0.8%) were catered for within the state system in special classes (Somerkivi, 1977). Within the state system there were

separate schools for children whose first language was Swedish (approximately 10%) but the same curriculum was followed. All children in the state system studied the same subjects for the first 4 years of schooling. At the end of Grade 4, when children were aged 11, each child was given a ranking score (*sijaluku)* based on the results of their summer examinations. This score helped to determine whether the child went on to high school (*oppikoulu)* which gave a more academic education, or remained at the elementary school for a further 4 years.

4.3.2 Methods and analysis

This paper examines only the results from the four years when all children studied a common programme. The 'core curriculum' subjects were: mathematics, religion, reading, writing, handcrafts, physical education and music. Additional subjects in Years 3-6 were geography, history, biology, Swedish (or Finnish if part of the 10% Swedish-speaking population), English or German, drawing and civics. In Years 7 and 8, practical subjects such as domestic science, agricultural studies, childcare, and book-keeping were taught. All pupils were given marks for conduct and attentiveness each year. There were two examinations per year, at Christmas and summer. I recorded only the results of the summer examinations. Marks given for each subject ranged from 4 (fail) to 10 (excellent). All pupils were given marks for conduct and attentiveness each year, and number of hours of absence without leave was recorded. Most children scored '10' for conduct, but a mark was deducted for transgressing school rules, (käytöksen alennus). It was considered a particular disgrace to score less than full marks for conduct and was an indicator of disruptive behaviour.

Tracing of school records cards

The names of the schools attended by all cases and controls were noted from the Child Health Cards. School record cards from the state elementary school system were traced for 400 cases and 408 controls in the Helsinki City Archives (83.1% of those who attended school in Helsinki). Of the 164 school record cards that could not be traced (86 cases and 78 controls): 20 cards had been destroyed during school fires, (17 cases and 3 controls) and 23 children had attended foreign language schools which are outside the state system (15 cases and 8 controls). I have no information on the remaining untraced cards (54 cases and 67 controls). It is possible that these subjects had moved away from Helsinki after starting their schooling and the card had been

transferred with them, or that they had moved school so frequently within Helsinki that the card had been lost or misfiled. Information from the school record cards was entered onto a specially-designed computerised database, blind to diagnosis. Subjects had attended 60 different elementary schools in Helsinki. I have information from at least one year of schooling on 400 cases and 408 controls, but numbers fluctuate slightly from year to year, due to migration to and from the city and emigration. Actual numbers of cases in each year 1-4 were: 384, 391, 380, and 367 respectively. Actual numbers of controls in each year 1-4 were: 382, 396, 376, and 361 respectively. There were no significant differences between numbers of cases and controls who had repeated a grade, and when these repeaters were excluded from the analysis the results did not change.

Statistical Analysis

Dichotomous variables, sex and social class (2 categories) were compared between cases and controls using chi-square tests. Ranking scores at the end of Grade 4 were compared between cases and controls using the t-test, and adjusted for sex and social group using regression analysis. Logistic regression was used to examine progression to high school adjusting for the confounding effects of sex and social group. The initial analysis of school exam results used logistic regression analysis with schizophrenia as the outcome measure and exam score in each school subject as a quantitative exposure. The odds ratio for schizophrenia was computed per examination grade for each school subject separately by year of schooling. All odds ratios were adjusted for sex and social class. All analyses were performed using the statistical program Stata 5.0 (Stata Corp., 1995). However this approach, (examining results in many subjects separately over 6 years) although beneficial in showing the effect of decrements in school scores on risk of schizophrenia was vulnerable to Type 11 errors. In addition this analysis did not take account of the clustering of pupils within schools. Therefore, in the next step, the data was reduced to three factor scores and analysed using multilevel modelling .

Principal components analysis (PCA) was used to reduce the school variables, including the behavioural measures, to a smaller number of underlying factors. Varimax rotation was used to make the results more interpretable. The criterion for significant loadings, by individual items, was set at 0.5. The second analysis was confined to school years 1-4 only when all children attended the same school system.

Multilevel modeling

The dependence of the three factors 'academic', 'non-academic' and 'behaviour' on case-control status and other covariates was then investigated using multilevel models (Goldstein, 1995).This method is a form of multiple linear regression which takes account of the hierarchical nature of the dataset, where individual measurement occasions are nested within pupils who in turn are nested within schools. Items nested within a higher level unit, (e,g, occasions within the same subject), tend to be inter-correlated because they are all affected by the same set of (unmeasured) influences specific to the higher level unit. Multilevel models allow for these correlations and deal efficiently with missing data. The method partitions the overall variance for each factor into a different component for each level in the hierarchy. The components in this analysis were: a between-school variance (level 3), a between-subject variance (level 2) and a within-subject (over time) variance (level 1). Case-control status, sex and social-group were entered as fixed effects. In order to examine interactions with case-control status, school year was included as a main effect (both continuous and categorical), and two interaction terms: case-by-grade, and case-by-sex were included in the model. Analyses were carried out using MLWiN 1.0 (Goldstein et al, 1998).

Correlates of school performance

To examine the clinical correlates of the three factor scores among the cases, age at onset of schizophrenia, mean annual number of days of hospitalization, and familial loading score were each divided into quintiles. Mean factor scores were computed for each quintile. Linear trends were examined using by entering quintile as a continuous variable into a multiple linear regression adjusted for sex and social group. P-values were corrected for clustering within person using robust methods (StataCorp, 1995).

Statistical Power

This study, with 400 cases and 408 controls had 80% power at 95% confidence to detect an increased risk of 50% (ie odds ratio 1.5) that the mean score for the cases would be half a grade below that of the controls (ie mean score 7.0 rather than 7.5).

4.3.3 Results

Characteristics of cases and controls on whom school record data is available

Table 4.1 shows that there was a significant excess of males among the cases compared with the controls (OR=1.6; 95% CI, 1.2-2.1). Cases and controls did not differ significantly on social class distribution. The mean age of onset of schizophrenia was 25.1 years (sd=5.5; range=13-40.1 years). The mean annual duration of hospitalization for schizophrenia was 50.2 days (sd=654; range = 0-309.4 days). The mean familial loading score for schizophrenia among the cases was 0.36 (sd=1.3; range= -0.61 to 5.89).

Table 4.1 Characteristics of Cases and Controls on whom school record data is available

Characteristic	Category	Cases n (%)	Controls n (%)	test statistic	p-value
Sex	male	249 (62.5)	209 (51.2)	9.99	0.002
Social class	1 (professional)	87	103	2.5	0.47
	2 (lower clerical)	45	39		
	3 (skilled manual)	221	220		
	4 (unskilled manual)	19	14		
Rank in class at age 11 yrs	mean (sd)	0.48 (.45)	0.52 (.29)	-1.3*	0.19
Destination	high school	194 (44.5)	242 (55.5)	10.5	0.001
	other	161 (56.9)	122 (43.1)		

· Adjusted for sex and social group (2 categories)

Rank in class (sijaluku) and progression to high school

In Finland, a child's rank in their class at the end of Grade 4 was termed the 'sijaluku' and was used to determine eligibility for entry to high school. For the purposes of this study, ranking scores were standardized for class size and ranged from 0.0 (last) to 1.0 (first). There was no difference between cases and controls on mean rank in their class at age 11 years, either before or after controlling for sex and social group, (Table 4.1). There was no difference in the proportion of cases compared with controls who came first in their class, (4.8% vs 4.4%; x^2=0.03, df=1, p=0.86), or last in their class (7.3% vs 8.6%; ^{2}=0.36, df=1; p=0.55). However, despite similar ranking scores, cases were only about half as likely as controls to proceed to high school after Grade 4, (OR(adjusted for sex and social group)=0.6; 95% CI, 0.44-0.82) (Table 4.1).

Teachers remarks on record cards

Additional remarks by teachers were noted on the report cards. These were coded as noting: (1) educational problems, (2) behavioural problems, (3) both educational and behavioural problems. No differences between cases and controls were found for any of these categories. Cases were significantly more likely than controls to been referred to a psychologist or psychiatrist (12 vs 4, x^2=4.2, p=0.04). Cases and controls were equally likely to have a note recording that a prize had been awarded.

School performance - examination results in individual subjects

'Core' curriculum subjects in Years 1 – 6

Table 4.2 gives logistic regression results for the risk of schizophrenia as predicted by the results in the 'core' curriculum subjects (reading, writing, maths, religion, handcrafts, sports and music). The table gives the odds ratio for case versus control status with each unit increase in score. All odds ratios were adjusted for sex and social class. Odds of schizophrenia did not vary significantly by results on reading or music in any year of schooling. Cases performed significantly more poorly than controls in sports in the first two years of schooling. Cases performed significantly more poorly than controls in handcrafts in the Year 2, with strong trends

for worse performance on handcrafts in Years 1 and 3 also. Cases performed more poorly than controls for religious education in Year 1 and Year 5 but these findings did not reach statistical significance. Cases performed significantly better than controls in writing exercises and mathematics in Year 6 only. This possibly reflects the differential progression to high school between the groups after Year 4.

Table 4.2 Logistic Regression Results for Cognitive Predictors of Risk for Schizophrenia in each School Year: (Core Curriculum Only) in School Years 1-6

Subject	**Odds ratios adjusted for sex and social class (with 95% confidence intervals)**					
	Year 1 (7-8 years)	**Year 2 (8-9 years)**	**Year 3 (9-10 yrs)**	**Year 4 (10-11yrs)**	**Year 5 (11-12yrs)**	**Year 6 (12-13yrs)**
Reading	1.06	1.08	0.95	0.98	0.82	1.00
	(0.92-1.22)	(0.9-1.24)	(0.8-1.1)	(0.8-1.15)	(0.6-1.06)	(0.7-1.35)
Writing	1.07	1.05	1.02	0.97	1.05	1.45**
	(0.9-1.21)	(0.9-1.18)	(0.9-1.16)	(0.8-1.1)	(0.8-1.32)	(1.1-1.9)
Maths	0.97	0.95	0.96	0.94	0.99	1.26
	(0.8-1.09)	(0.8-1.05)	(0.8-1.07)	(0.8-1.05)	(0.8-1.2)	(1.0-1.6)
Religion	0.82	0.89	0.90	0.98	0.79	1.06
	(0.7-1.01)	(0.7-1.07)	(0.8-1.05)	(0.8-1.13)	(0.6-1.01)	(0.7-1.43)
Handcrafts	0.85	0.83*	0.87	0.89	0.92	0.95
	(0.7-1.00)	(0.7-0.97)	(0.74-1.0)	(0.7-1.05)	(0.7-1.16)	(0.7-1.3)
Sports	0.71**	0.69 **	0.86	0.87	0.86	0.75
	(0.5-0.89)	(0.5-0.85)	(0.7-1.04)	(0.7-1.03)	(0.6-1.12)	(0.6-1.0)
Music	1.01	0.97	0.94	0.98	0.96	0.93
	(0.8-1.18)	(0.8-1.13)	(0.8-1.09)	(0.8-1.14)	(0.7-1.2)	(0.7-1.24)

*p<0.05, **p<0.01

'Additional' subjects in Years 3 – 6

There were no significant differences in performance between cases and controls for the additional subjects studied in Years 3 – 6 (drawing, Swedish, English, civics, geography, biology) (Table 4.3)

Table 4.3 Logistic Regression Results of Cognitive Predictors of Schizophrenia in each School Year: Additional Subjects in School Years 3-6

Subject	Odds ratios adjusted for sex and social group (with 95% C.I)			
	Year 3 (9-10 yrs)	**Year 4 (10-11yrs)**	**Year 5 (11-12yrs)**	**Year 6 (12-13yrs)**
Drawing	1.04 (0.87-1.25)	0.98 (0.83-1.16)	1.12 (0.86-1.48)	1.18 (0.86-1.63)
Swedish	0.84 (0.64-1.11)	0.91 (0.72-1.16)	0.80 (0.49-1.3)	0.65 (0.36-1.19)
English	1.23 (0.92-1.65)	1.21 (0.96-1.52)	1.35 (0.86-2.12)	1.79 (0.94-3.39)
Civics	0.99 (0.72-1.35)	0.82 (0.63-1.07)	0.94 (0.63-1.41)	0.85 (0.51-1.44)
Geography	0.92 (0.81-1.04)	0.94 (0.84-1.07)	1.09 (0.89-1.36)	1.05 (0.81-1.4)
Biology	-	0.91 (0.78-1.05)	0.81 (0.62-1.04)	1.12 (0.86-1.45)

'Practical' subjects in Years 7-8

There were no significant differences between cases and controls in school performance during Years 7-8 (Table 4.4). These years were meant to prepare the children for the realities of adult life and had a strong emphasis on practical subjects such as childcare and domestic science (for girls) and agricultural studies (for boys).

Table 4.4 Logistic Regression Results of Cognitive Predictors of Schizophrenia: 'Practical' Subjects in School Years 7 and 8

Subject	Odds Ratios adjusted for sex and social group (with 95% C.I)	
	Year 7 (13-14 yrs)	**Year 8(14-15 yrs)**
Reading	0.53 (0.28-1.01)	0.69 (0.36-1.34)
Writing	1.25 (0.70-2.23)	1.85 (0.74-4.1)
Mathematics	1.07 (0.84-1.39)	1.17 (0.92-1.5)
Career guidance	0.94 (0.58-1.54)	0.83 (0.51-1.37)
Childcare	0.76 (0.54-1.06)	0.95 (0.69-1.27)
Social studies	0.44 (0.17-1.09)	0.93 (0.41-2.04)
Domestic science/agriculture	1.03 (0.75-1.42)	1.12 (0.77-1.62)
Health studies	1.13 (0.88-1.45)	1.19 (0.93-1.52)
Civics	0.94 (0.66-1.34)	0.92 (0.66-1.28)
English	0.72 (0.47-1.09)	0.82 (0.52-1.28)
Swedish	0.91 (0.67-1.23)	0.93 (0.70-1.23)
Sports	0.97 (0.76-1.23)	1.21 (0.94-1.56)

Conduct, attentiveness and absences from school

There were no differences between cases and controls on mean conduct or attentiveness scores in any year of schooling either before or after adjustment for sex and social group. Cases had significantly more hours of absence from school recorded in Year 4 [31.5 (sd=40.9) vs 25.7 (sd=25.1); t=2.05 df=580; p=0.04], and Year 7 [70.3 (sd=88.6) vs 47.1 (sd=44.4); t=2.15 (df=185) p=0.03]. However after adjustment for sex and social class these differences were no longer statistically significant.

Principal components analysis: School Factor Scores

The 'core curriculum subjects were entered into a principal components analysis. This yielded three factors with eigenvalues greater than 1.0: an academic factor, a behavioural factor and a non-academic factor. The subjects that loaded onto each factor are shown in Table 4.5. The results in relevant individual subjects were summed to derive separate the academic and non-academic scores, and the factor scores were used to create the behaviour score. High scores in the academic and non-academic factors indicate better performance. A high score in the behavioural factor indicates poor behaviour. There was a strong positive correlation (0.47) between the academic and the non-academic factors (Table 4.6). The correlations between the academic and the behavioural factors, and the non-academic and the behavioural factors did not exceed 0.1.

Table 4.5 Principal Components Analysis of School Subject Scores (with Varimax Rotation)

School subjects	Factor 1 (Academic)	Factor 2 (Behavioural)	Factor 3 (Non-academic)
Conduct	0.14	**-0.73**	-0.15
Absences (hrs)	0.04	**0.69**	-0.24
Attentiveness	**0.68**	-0.27	0.16
Mathematics	**0.79**	-0.08	0.13
Reading	**0.79**	0.11	0.03
Writing	**0.87**	-0.01	0.11
Religion	**0.75**	-0.08	0.18
Handcrafts	0.44	-0.21	**0.51**
Sports	0.13	-0.20	**0.82**
Eigenvalue (% variance explained)	3.6 (40.5)	1.13 (12.5)	1.01 (11.0)

Table 4.6 Correlational analyses of interrelationships between measures of school performance (A=academic, B=behavioural, N=Non-academic) *=significant correlations

	Total sample		Cases only		Controls only	
	A	N	A	N	A	N
N	0.47*		0.46*		0.48*	
B	-0.09*	-0.05*	-0.04	-0.016	-0.14*	-0.09*

Multilevel modeling: Comparison of school performance (factor scores) between cases and controls

Table 4.7 shows the results of multilevel modelling of school performance in the three factor scores in cases compared with controls. There was a significant main effect for case-control status for the non-academic factor only - cases performed significantly worse than controls. There was no significant main effect for case-control status for the academic or the behaviour scores. There were no significant main effects for sex, but there was a trend towards better performance in academic subjects by females. There were significant effects for social group on all factors. Social groups 1 and 2 performed better than social groups 3 and 4 on the academic and non-academic factor scores, but worse in the behaviour factor. Interaction terms, case-by-sex, and case-by-grade, were not significant for any of the three factors.

There was no significant variance between schools on the academic, non-academic or behavioural factor scores. The percentage of residual variance due to between-subject variation (intra-class correlation) was 77% of the variance in the academic and behavioural factor scores, and 60% of the variance in the non-academic factor (Table 4.7).

Correlates of factor scores

Table 4.8 presents the correlates of the factor scores among the cases. There was no influence of age-at-onset, severity of illness or genetic risk for schizophrenia on results for any of the three factors.

Table 4.7: Results of multilevel modelling of school performance

Variable	**Academic score**		**'Non-academic'score**		**'Behavioural' score**	
Fixed	*Estimate (SE)*	*p-value*	*Estimate*	*SE*	*Estimate*	*SE*
Case [a]	-0.36 (0.3)	0.29	-0.34 (0.1)	<0.001	-0.01 (0.05)	0.9
Sex [b]	0.59 (0.35)	0.09	0.07 (0.1)	0.5	-0.01 (0.05)	0.9
SEG [c]	-2.6 (0.3)	<0.001	-0.33 (0.1)	0.002	-0.15 (0.05)	0.003
Variances		*%*		*%*		*%*
Within student	4.5 (0.18)	23	0.8 (0.03)	39.5	0.17 (0.02)	23
Between student	14.7 (0.9)	77	1.2 (0.1)	60.5	0.6 (0.02)	77
Between schools	0		0		0	

Baseline categories for which dummy variables are estimated against: [a] control; [b] male; [c] social groups 1&2.

Table 4.8 The Relationship between School Performance Scores (Years 1-4) and Indices of Illness Severity and Genetic Risk among Schizophrenic Patients.

	Quintile (n)	Range (yrs)	Academic score mean (sd) *	Non-academic score mean (sd) *	Behavioural factor score. mean (sd) *
Age at onset	1 (79)	13-20.5	38.7 (4.1)	14.7 (1.4)	-0.011 (0.7)
	2 (79)	20.6-23.1	38.2 (4.5)	14.9 (1.2)	-0.0009 (1.3)
	3 (79)	23.1-26.1	37.8 (4.7)	14.9 (1.3)	-0.006 (1.2)
	4 (79)	26.1-29.9	38.9 (4.6)	14.8 (1.4)	0.006 (0.8)
	5 (79)	29.9-40.1	38.1 (3.7)	14.7 (1.3)	0.115 (0.8)
Familial Loading score	1 (78)	-.61 to -.31	37.8 (4.8)	15.0 (1.4)	0.18 (1.5)
	2 (78)	-.31 to -.26	38.6 (4.2)	14.9 (1.3)	-0.10 (0.5)
	3 (77)	-.26 to -.22	38.7 (4.3)	14.7 (1.3)	-0.06 (0.5)
	4 (78)	-.22 to -.1	38.5 (4.0)	14.8 (1.2)	-0.05 (0.8)
	5 (78)	-0.1 to 5.9	38.2 (4.3)	14.7 (1.3)	0.35 (1.2)
Chronicity **	1 (77)	0 to 6.5	39.3 (3.9)	14.9 (1.3)	0.03 (1.2)
	2 (76)	6.5 to 17.3	38.0 (4.4)	14.8 (1.3)	-0.003 (0.7)
	3 (76)	17.3 to 37.3	38.6 (4.5)	14.9 (1.3)	-0.09 (0.6)
	4 (76)	38.2 to 70.3	37.9 (4.6)	14.8 (1.3)	-0.25 (0.8)
	5 (76)	71 to 309.4	38.0 (4.1)	14.8 (1.4)	0.08 (1.4)

* Tests for linear trend not significant. ** Average annual duration of hospitalisation in days

4.3.4 Discussion

Methodological issues

The purpose of this section is to focus on specific methodological concerns regarding the studies presented in this chapter.

The first consideration concerns the choice of study design. This study set out to be a 'nested case control study – in other words a case-control study nested within a 10-year birth cohort of everyone born in Helsinki between 1951 and 1960. However, the controls were not selected from the birth register but from the child health clinic archive. Therefore the study is actually a case-control study nested within a 'hypothetical' cohort of individuals who were born in Helsinki between 1951 and 1960 *and* who attended child health clinics in Helsinki.

The second consideration concerns the possibility of bias due to migration. Information on the cases was ascertained from national registers. In order to be listed on these registers the case must have been admitted to a hospital in Finland or have applied for free medicine or a disability pension. In contrast there is no information on the adult outcome of the controls except that they were never on any of these registers with a diagnosis of schizophrenia in adulthood. This does not discount the possibility that some of the controls emigrated and possibly developed schizophrenia in adulthood elsewhere. However the emigration rate in Finland between 1951 and 1960 averaged at about 0.16% (http://www.utu.fi/erill/instmigr/eng/e_02.htm and http://www.library.uu.nl/wesp/populstat/Europe/finlandc.htm). Therefore only about 66 of the controls are likely to have emigrated, of whom one would expect only 1% (6 or 7 individuals) at most, to have subsequently developed schizophrenia. This possible misclassification bias would not have led to any spurious positive associations and is unlikely to have greatly influenced the highly statistically significant ($p<0.001$) negative association between non-academic performance and later schizophrenia found in this study.

The third potential limitation of the study is the potential for Type 11 errors due to the analysis of 7 different school subjects over 6 years (see Table 4.2). In an effort to deal with this problem I then carried out a principal components analysis which reduced 7 subjects to 3 factors. These

factors were then entered into a multilevel modelling analysis which took account of the repeated nature of the data. The poorer performance by cases in non-academic subjects remained highly significant under this more rigorous analysis.

The findings

The first hypothesis that children who would later develop schizophrenia would perform worse in academic subjects was not upheld. Preschizophrenic children were rated as performing just as well as their peers in academic subjects throughout the school grades. This was unexpected as previous studies, mainly of case-control design, have found lower childhood IQ among schizophrenic patients (Aylward et al, 1984), and have shown an inverse linear relationship between low IQ in childhood (Jones et al, 1994; Done et al, 1994) and adolescence (David et al, 1997) and risk of schizophrenia.

There are several possible explanations for this discrepancy. (1) The Finnish school system during the 1950s and 60s, was very structured, with standardised teaching methods, rigid adherence to the curriculum, and strong social pressure to conform to behavioural and social norms. The preschizophrenic child may perform well academically in such an ordered and predictable environment. A recent analysis of school performance as a predictor of later psychiatric illness in the 1966 North Finland Birth cohort supports these results: there was no difference in examination results at age 16 years between the preschizophrenic children and non-hospitalised general population comparison group, (Isohanni et al, 1998). (2) The current sample included some cases with schizoaffective disorder and schizophreniform disorder, these are putatively less severe illnesses than schizophrenia and such cases may have performed better in school. However, I found no relationship between academic ability and severity of illness, so it is unlikely that these cases influenced the results. (3) Most other studies examining this issue have used specialised educational tests or IQ tests administered by trained personnel. Such tests are likely to pick up subtler cognitive abnormalities than can be detected from routine school grades. However school exam results have the advantage of being a practical, 'working' measure of intelligence among school-children in their normal environment, rated by their own teachers. Pre-schizophrenic children may perform better in such familiar circumstances than in an artificial test situation which may induce more anxiety. (4) There is evidence that high-risk children who experience non-optimal rearing environments show greater childhood impairments (Mednick and Schulsinger, 1968; Parnas et al, 1985; Tienari, 1991). The current sample included only those

cases who were both born and educated in Helsinki city, thus excluding some children with unstable family environments and residential instability. However, the sample contained children who moved frequently but remained within Helsinki city, and the analysis controlled, as far as possible, for factors which might influence migration by using non-migratory controls.

The second hypothesis, that children who would later develop schizophrenia would show more behavioural problems than controls was also not upheld. Again the explanation may reside in the high standards of behaviour expected at school at that time and perhaps the rather conformist nature of the Finnish personality. It was considered a particular disgrace to score less than '10' for conduct and teachers did not give this punishment lightly. There was little space on the school report cards for free comments by the teacher and, under such circumstances, the comments that do exist may indicate just as much about the teacher's personality as the pupil's behaviour. It is possible that had standardised, detailed teacher's ratings of behaviour been available, as in previous studies (Watt, 1978; 1974; Done et al, 1994; Olin et al, 1995) that subtle behavioural differences between cases and controls would have emerged.

The unexpected 'positive' finding was that children who develop schizophrenia in adulthood perform significantly worse than their peers on sports and handcrafts (the non-academic factor). One explanation is that sports and handcrafts test co-ordination skills, and that pre-schizophrenic children show deficits in motor co-ordination when compared with their peers. This finding is actually not so surprising when one reviews the literature on childhood development and later schizophrenia as outlined in chapter 3. Firstly, analyses from the British birth cohorts have shown that children who went on to develop schizophrenia showed delayed motor milestones in infancy, were noted as being 'poor at games and physical activities' at age 13, and showed an excess of twitches and grimaces at age 15 (Jones et al, 1995), had poorer coordination than their peers at age 7, and were rated as significantly clumsy at age 16 (Crow et al, 1995). Secondly, motor co-ordination deficits are the most consistently found indicator of dysfunction in middle childhood among studies examining children at high risk for schizophrenia (Mednick & Silverton, 1988; Hans & Marcus, 1991; Marcus et al, 1997, and evidence is now accumulating that such motor abnormalities predict later schizophrenia or schizophrenia-spectrum disorders (Fish et al, 1992; Erlenmeyer-Kimling et al, 1992; Lafosse, 1994). Thirdly, the 'home-movie' studies of Walker and colleagues also show neuromotor abnormalities preceding schizophrenia, primarily left-sided choreoathetoid movements and posturing and were noted only up to 2 years old (Walker & Levine, 1990; Walker et al, 1994). The difficulties with sports and handcrafts

were more prominent at earlier ages in the current study (see Table 4.2) and this may indicate a delay in learning or automatising new skills, particularly those at the 'cusp of development' (Asarnow et al, 1995).

However an alternative explanation is that poor performance in sports and handcrafts may be due to personality/ motivational factors. In structured setting, such as mathematics class, individual differences may be minimised by situational pressures to conform. Sports and handcrafts are 'softer' subjects which represent the more social, unstructured aspects of the curriculum and reflect other abilities such as artistic ability and teamwork. It may be these aspects of school life which preschizophrenic children find particularly difficult, and in which they express early schizoid tendencies. Previous case-control, (Offord and Cross, 1969; Rutter, 1984; Cannon et al, 1997) and cohort (Malmberg et al, 1998, Davidson et al, 1999) studies have described poor premorbid adjustment and poor social functioning in childhood among individuals with schizophrenia, and significant behavioural differences from peers.

My finding that pre-schizophrenic children were less likely than controls to progress to high school also provides support for childhood personality/motivational problems in schizophrenia. Many cases who were eligible to move into the academic 'stream', by virtue of their ranking score in the grade 4 exam, chose instead to stay on at the elementary school for a further 4 years to finish their education. I do not know whether the preschizophrenic children were themselves reluctant to proceed, or were discouraged from doing so by parents or teachers. The high school was perceived at that time as a more stressful and demanding environment than the elementary school. Failure to finish school (Keith et al, 1991) and 'lack of academic or vocational ambition' (Hartman et al, 1984), have been noted previously as risk factors for schizophrenia. In the 1966 North Finland birth cohort the proportion of preschizophrenic children 'not in normal class' at age 14 was about three times higher than in the comparison group (Isohanni et al, 1998).

On balance I favour the motor co-ordination explanation, rather than the personality/motivational explanation, for the poor performance in non-academic subjects among the preschizophrenic children. The Finnish elementary school curriculum during the 1950's and 1960's placed a great deal of emphasis on sports and handcrafts - at least 4 hours per week was devoted to these activities and there was a rigorous schedule of skills and crafts to be mastered (Table 4.9). The emphasis was on the acquisition of skills, (such as catching, skiing, skating and gymnastics), rather than team sports, particularly in the early years of schooling. Children were graded on

their athletic ability or the quality of their handcrafts rather than on perceived 'effort' or 'team spirit'. Of course the most parsimonious explanation, and the most difficult to disprove, is that my findings represent both motor co-ordination deficits and poor psychosocial adjustment in children who later develop schizophrenia. These findings replicate the results from the studies discussed in Chapter 3, but within a much larger epidemiological sample, and confirm that poor motor coordination in childhood is a risk factor for adult schizophrenia.

Table 4.9. Finnish elementary school curriculum: Sports and Physical exercise

Grade	*Period*	**Schedule**
1 & 2	Autumn and Spring outdoor sports period	Athletics exercises; Catching and throwing exercises incorporated into children's games
	Autumn and Spring indoor sports period	Gymnastics and physical exercises according to the schedule; games involving music and physical exercise.
	Winter sports period	Skiing and skating
3 & 4	Autumn and Spring outdoor sports period	Boys: Athletics training including triathlon and relay races; Finnish baseball and football; cross-country races and orienteering. Girls: Relay races and athletics exercises; Finnish baseball; Cross country races and orienteering.
	Autumn indoor sports period	Gymnastics and physical exercises according to schedule; Boys: 20 -30 minutes must be spent on gymnastic apparatus. Girls: Separate classes for sports and for music exercises and traditional dance.
	Winter sports period	Exercises as before, Skiing, skating; bandy (boys only)

4.4 An investigation of obstetric complications as risk factors for schizophrenia in a Finnish population-based sample

4.4.1 Introduction

As outlined in Chapter 2, obstetric complications have long been linked to risk of later developing schizophrenia but many of the studies examining this issue have been prone to biases of various types. In this study I aimed to examine the association between obstetric complications and later schizophrenia in a large population-based case control study with use of record linkage techniques to identify the cases from national health registers and to obtain prospectively-recorded information from archived birth records. In this way the study would be relatively free from selection and information bias. In addition, the sample size would be large enough to allow examination of individual complications as risk factors for later schizophrenia.

The Finnish obstetric system

Before World War II, Finnish women normally gave birth at home. In 1938, 50% were helped by midwives in their homes, 17% gave birth without any trained medical help, and 33% gave birth in hospital (Hemminiki, 1983). The proportion of hospital deliveries increased rapidly after 1945, to 58% in 1950, 77.9% in 1955 and 92.5 % in 1960. Infant mortality decreased from 48.3% in 1950 to 7.6% in 1979.There are three large maternity units in Helsinki which have been established since the 1940's: Naistenklinikka 1 and Naistenklinikka 2, the maternity departments of the Central University Hospital of Helsinki and Kätilöopisto, a training hospital for midwives. Detailed birth records have been completed by the midwives on all women who have given birth in these units using similar standardised forms. Birth records from Naistenklinikka are stored in the archives of the Helsinki University Central Hospital and birth records for Kätilöopisto are stored in the Helsinki City Archives. The records cover the time from admission to the maternity unit until discharge. The first section of the birth record gives demographic information about the mother and a summary of any complications during the pregnancy; the second section describes the examination of the mother by the midwife on admission; the third section details the course of the delivery, and the last section describes the condition of the infant at birth, including

measurements of length, head circumference, placental weight and birth weight, and the infant's neonatal progress.

4.4.2 Methods and analysis

Subjects

The study population comprised all individuals who were born in Helsinki, Finland between 1951 and 60. Cases of schizophrenia born during this period were ascertained from three national health care registers, as outlined in Section 4.3. In total 928 individuals were identified from the registers who had received a '295' diagnosis of schizophrenia and who were born between 1951 and 1960. The controls ascertained for the school record study were used in this study also (see Section 4.3). These comprised 486 individuals who were born in Helsinki between 1951 and 1960 who had not received a '295' diagnosis. The name and date-of-birth for controls was obtained from their Child Health record cards stored in the Helsinki City Archives. The controls were frequency matched to the cases in the school record study only on year of birth. Therefore I felt that they could be considered a random sample of the general population born in Helsinki within the study period.

Tracing of birth records

Accordingly, birth records were sought for 928 cases and 486 controls in the archives of the Helsinki University Central Hospital and in the Helsinki City Archives. Records were traced by using the information on child's date of birth and mother's name and date of birth. Birth record data was entered onto a specially-designed computer database, following the standardised format of the records. We succeeded in locating birth records for 636 cases (68.5%) and 203 controls (41.7%). There was no difference in the proportions of the case and control groups who were born in each of the three units. The reason for the lower tracing rate in controls is that we did not have full information on mother's name and date of birth in this group. The schizophrenia group was ascertained from a case register where identifying information on the mother was obtained from linkage with the population register, whereas the control group was ascertained from the child health records stored in the Helsinki city Archive - the mother's full name and date of birth was often not recorded on these cards.

Statistical Analysis

Dichotomous variables, sex and social class (2 categories) were compared between cases and controls using chi-square tests. Odds ratios (ORs) and 95% confidence intervals for schizophrenia in relation to individual complications were calculated and adjusted for possible confounding variables. Obstetric complications thought to indicate perinatal hypoxia were assessed using the scale of Cannon TD et al (2000b).

Continuous variables were divided into categories that corresponded to previous published work – to allow direct comparison. Ponderal index (birthweight / (length)^3) is a measure of thinness at birth and was calculated for all subjects. Analysis of continuous variables in quartile groups (related to the distribution in the controls) was also carried out and tests for linear trend were applied where appropriate. Analyses were carried out using STATA version 5.0 (StataCorp. 1995).

Power: For an exposure at 10% prevalence in the control group, this study had 90% power with 90% confidence to detect an odds ratio of 2.0 and 40% power at 90% confidence to detect an odds ratio of 1.5. Power calculations were performed using Epi-Info (Dean et al, 1990).

4.4.3 Results

Missing data

Using the data from the school record study I examined the socio-demographic characteristics of the controls with missing data compared with the controls for whom we found birth records. There were no differences between the traced and untraced controls on sex or school performance. Controls for whom I could not trace birth records were more likely to come from the professional/managerial social class (SEG 1) than those for whom records were traced (30.7% vs 22.8%, x^2=7.1, df=3, p=0.07), although this difference was not statistically significant at the 5% level. There was also a trend for 'missing' cases to be from the highest social class (30.2% vs 21%, x^2=6.4, df=3, p=0.09). There were no differences in chronicity or age at onset for schizophrenia between the traced and untraced cases. It is likely that the higher social classes were more likely to give birth in smaller units (headed by general practitioners) or at home

compared with the large maternity hospital (Hemminki, 1983). In 1965 23% of all births took place in such small units. Since this process appears to apply to the mothers of both cases and controls it should not bias the comparison between the groups.

Sex and social class distribution of cases and controls

There was no significant difference in the social class distribution of cases and controls for whom birth records were available, (x^2=0.7,df=3, p=0.9). There were significantly more males among the cases than controls (OR 1.78: 95% CI:1.3-2.5).

Table 4.10 Sociodemographic characteristic of cases and controls for whom birth records were available

	Cases (n=636)	**Controls (n=201)**	**OR (95% ci)**
Categorical variables			
Male sex (child)	382 (60.1)	92 (45.8)	1.78 (1.3-2.5)
SEG I &II	189 (31.3)	62 (31.4)	0.99 (0.7-1.4)

Maternal characteristics

Maternal characteristics are shown in Table 4.11. Mothers of cases differed from the mothers of controls on two variables: (1) *Overall impression on admission* - mothers of cases were twice as likely as mothers of controls to be rated as being in poor or moderate condition by the midwife on admission to the delivery unit; (2) *Haemoglobin* - Mothers of cases had lower haemoglobin than mothers of controls at the last antenatal visit.

There were no differences between the groups for maternal weight, maternal height, length of admission, maternal age or parity. There was no relationship between familial loading score for schizophrenia and overall impression of the mother by the midwife. None of the mothers were psychotic during the pregnancy.

Table 4. 11 Characteristics of the mothers of cases and controls

	Cases (n=636)	**Controls (n=201)**		
Categorical variables			*OR (95% ci)*	*OR adj. for SEG*
Moderate/poor impression	54 (8.8)	8 (4.04)	2.3 (1.1-4.9)	2.23 (1.03-4.8)
Continuous variables			*t (df)*	*p-value*
Maternal age (years)	28.3 (0.2)	28.02 (0.4)	-0.53 (835)	0.59
Parity	1.92 (0.04)	1.92 (0.08)	0.06 (822)	0.95
BMI late pregnancy (kg/m^2)	26.9 (0.1)	27.0 (0.2)	0.33 (784)	0.74
Wgt. increase in preg. (kgs)	12.6 (0.3)	13.6 (0.6)	2.01 (232)	0.16
Haemoglobin in late pregnancy	71.4 (0.4)	75.9 (2.3)	8.2 (610)	0.004**
Length of labour	23.8 (8.2)	24.7 (10.2)	0.06 (808)	0.95
Length of stay in hosp. (days)	6.8 (0.71)	6.1 (0.8)	0.52 (828)	0.6

**Adjusted for SEG and sex of child: F=6.7, p=0.01

Pregnancy and delivery variables

Table 4.12 shows that there were no statistically significant differences between cases and controls for any of the pregnancy and delivery and neonatal variables recorded in the birth records. There was a trend for more rhesus/ABO incompatibility among cases (1.6% vs 0, x^2 =3.2, p=0.07).

Table 4.12 Pregnancy and delivery variables

Pregnancy and delivery	Cases (n=636) N (%)	Controls (n=201) N (%)	Crude OR (95% CI)	OR adjusted for sex and seg (95% CI)
Pre-eclampsia	6 (0.94)	1 (0.5)	1.9 (0.23-15.9)	1.97 (0.2-16.7)
Diabetes	3 (0.47)	0.00	…	
Bleeding (all trim)	23 (3.6)	7 (3.48)	1.03 (0.4-2.4)	1.04 (0.43-2.5)
Fever (all trim)	15 (2.4)	1 (0.5)	4.39 (0.6-36.8)	4.9 (0.6-37.8)
Influenza (all trim)	10 (1.6)	2 (1.0)	1.6 (0.34-7.3)	1.6 (0.34-7.6)
Rhesus/ABO incomp.	10 (1.57)	0	..	..
Transfusion/jaundice	14 (2.2)	4 (1.9)	1.1 (0.4-3.4)	1.4 (0.4-4.3)
Premature (<37wks)	31 (4.9)	10 (4.9)	0.97 (0.5-2.03)	0.98 (0.452.1)
Abnormal presentation	19 (3.3)	10 (5.7)	0.57 (0.2-1.2)	0.59 (0.2-1.3)
Caesarian section	29 (4.6)	10 (4.9)	0.91 (0.4-1.9)	0.87 (0.4-1.8)
Forceps delivery	12 (1.9)	1 (0.5)	3.84 (0.5-29.8)	3.2 (0.4-25.8)
Cephalo-pelvic disprop.	10 (1.6)	1 (0.5)	3.2 (0.4-25.11)	2.6 (0.32-20.6)
Uterine exhaustion	12 (1.9)	4 (1.9)	0.9 (0.3-2.9)	0.8 (0.2 -2.6)
Threatened asphyxia	19 (2.99)	4 (1.99)	1.5 (0.5-4.5)	1.3 (0.42-3.9)
Transfer to special unit	29 (4.6)	7 (3.5)	1.3 (0.6-3.1)	1.3 (0.6-3.1)
Twin birth	25 (3.93)	4 (1.99)	2.01 (0.7-5.8)	1.94 (0.6-5.6)
Incubator	11 (1.73)	7 (3.48)	0.5 (0.1-1.27)	0.5 (0.2-1.3)
Birthweight<2500g	27 (4.3)	9 (4.9)	0.9 (0.4-2.05)	0.9 (0.4-2.0)

Perinatal hypoxia

Obstetric complications thought to indicate perinatal hypoxia were assessed using the scale of Cannon TD et al (2000a). This scale has been used in a Finnish sample (Rosso et al, 2000). The eleven complications comprising the scale are presented in Table 4.13. There were no differences between the cases and controls on any of the complications separately or on the total score. There were no significant relationships between perinatal hypoxia score and sex, age at onset or familial loading score.

Table 4.13 Distribution of complications indicating perinatal hypoxia among cases and controls

Perinatal hypoxia variables	Cases (n=636) N (%)	Controls (n=201) N (%)	Crude OR (95% CI)	OR adjusted for sex (95% CI)
'Blue' colour, first 5 mins	18 (2.8)	6 (2.9)	0.9 (0.4-2.4)	0.8 (0.3-2.3)
Cyanosis noted	25 (3.9)	10 (4.9)	0.8 (0.4-1.6)	0.8 (0.4-1.6)
Abn. fetal heart rate or rhythm	19 (2.9)	4 (1.9)	1.5 (0.5-4.5)	1.4 (0.5-4.1)
Required resuscitation or oxygen	22 (3.5)	13 (6.5)	0.5 (0.2-1.0)	0.6 (0.2-1.1)
Other respiratory abnormalities	6 (0.9)	3 (1.5)	0.6 (0.1-2.5)	0.6 (0.2-3.1)
Bleeding in third trimester	36 (5.6)	16 (7.9)	0.7 (0.4-1.3)	0.7 (0.4-1.2)
Polyhydramnios	41 (6.5)	8 (3.9)	0.7 (0.8-3.6)	1.7 (0.7-3.7)
Cord abnormalities *	146 (22.9)	48 (23.9)	0.9 (0.6-1.4)	0.9 (0.6-1.4)
Meconium in amniotic fluid	102 (16.0)	28 (13.9)	1.2 (0.7-1.8)	1.2 (0.8-1.9)
Placental abnormalities **	54 (8.5)	16 (7.9)	1.01(0.6-1.9)	0.9 (0.5-1.7)
Thoracic abnormalities	2 (0.3)	0	-	-

*cord around neck or body, tied in knot; **thrombosis, villous lesions, abruptio placenta

Placental and neonatal measurements: Indicators of fetal growth impairment

Table 4.14 shows the neonatal measurements of the children in both groups. Ponderal index (birthweight / (length)^3) is a measure of thinness at birth. The cases had significantly lower mean birth weight and lower mean ponderal index (PI) than the control children. There were no differences between the groups for head circumference or length. The nature of the relationship between birthweight and ponderal index (separately) with later schizophrenia was analysed using quartiles. Table 4.15 shows the results of the quartile analysis. There is a significant inverse linear relationship between risk of later schizophrenia and both low ponderal index and low birth weight in that the lower the PI or birth weight, the greater the risk of developing schizophrenia. Individuals in the lowest quartile for PI or birth weight have about twice the risk of developing schizophrenia than individuals in the highest quartile. This relationship was not changed when the odds ratios were adjusted for prematurity (<37 weeks), or when individuals with premature births were excluded from the analysis.

Table 4.14 Measures of placental growth, fetal growth, head size and birth weight

Child characteristics	Cases (n=636) Mean (SE)	Controls (n=201) mean (SE)	t-test (df)	p-value
Birthweight (g)	3418.5 (21.7)	3511.5 (39.8)	4.35 (1,833)	0.04
Length (cm)	50.15 (0.08)	50.26 (0.13)	0.7 (1,825)	0.47
Ponderal index (kg/m^3)	27.04 (0.095)	27.65 (0.16)	9.71 (1,825)	0.002
Head circumference (cm)	34.84 (0.06)	34.88 (0.09)	0.36 (1,669)	0.71
Placental size 1 (cm)	17.7 (0.17)	17.74 (0.17)	0.02 (1,811)	0.98
Placental size 2 (cm)	18.8 (0.11)	18.75 (0.1)	-0.17 (1,811)	0.86
Placental weight (g)	645.6 (12.7)	670.5 (24.9)	0.93 (1,816)	0.34

Table 4.15 Ponderal Index and birth weight (in quartiles) and odds ratios for schizophrenia

Quartile (Range)	No. controls (%)	No. cases (%)	OR crude (95% CI)	OR (excl. Prem. births) (95% CI)	OR adjusted * (excl. prem. births) (95% CI)
Ponderal Index (kg/m^3)					
1	16.3-26.39	49 (25)	257 (40.9)	2.1 (1.4-3.3)	2.4 (1.5-3.8)	2.1 (1.3-3.5)
2	26.4-27.87	50 (25)	133 (21.1)	1.1 (0.7-1.7)	1.1 (0.7-1.7)	0.95 (0.6-1.6)
3	27.89-28.9	49 (25)	116 (18.4)	0.9 (0.6-1.5)	0.9 (0.6-1.5)	0.9 (0.5-1.5)
4	29.0-35.5	50 (25)	123 (19.6)	baseline	baseline	baseline
Test for trend				Z = -3.53 p<0.001	z= -3.77 P<0.001	Z= -3.1 P=0.002
Birthweight (g)						
1	950-3219g	50 (25)	221 (34.8)	2.0 (1.3- 3.2)	2.2 (1.3-3.5)	2.46 (1.5-4.1)
2	3220-3539	50 (25)	145 (22.9)	1.3 (0.8-2.1)	1.3 (0.8-2.1)	1.33 (0.8-2.2)
3	3540-3899	51 (25)	156 (24.6)	1.3(0.8- 2.1)	1.3 (0.8-2.1)	1.49 (0.9-2.5)
4	3900-5000	50 (25)	112 (17.7)	baseline	baseline	baseline
Test for trend				Z= -2.9 p<0.001	Z= -3.02 P=0.003	Z= -3.1 P=0.002

*Adjusted for sex, socio-economic group (4 categories), year of birth, maternity unit (3 categories) and maternal body mass index (continuous)

Relationship between obstetric factors and school performance

In order to investigate whether the association observed in the first study between poor performance in sports and handcrafts could be explained by low birth weight or low ponderal index, a logistic regression was carried out examining the risk of schizophrenia in relation to performance in the academic, nonacademic and behavioural factors after adjustment for

birthweight and ponderal index. Addition of the obstetric variables to the model made no difference to the strength of the association between the non-academic school factor and later schizophrenia.

4.4.4 Discussion

Methodological issues

This study had several methodological advantages for the investigation of the relationship between obstetric complications and later schizophrenia. Information was obtained from prospectively-recorded birth records which were unbiased by the later outcome. Cases were obtained from an epidemiological sample ascertained from three national healthcare registers. The cases had passed through the period of risk for schizophrenia – unlike other studies which have examined early onset cases only. The number of cases is large giving high statistical power to examine small effects (odds ratio 2.0) and quantitative relationships.

Limitations

This study was restricted to births in the major maternity units in Helsinki, Finland during the 1950's. This would introduce a bias if the associations between low ponderal index, low birth weight and schizophrenia differed between those born in the hospital and those born outside hospital or in smaller units. Analysis of the 'missing' data shows that women from the highest social class were less likely to give birth in the large maternity hospitals. However this applied equally to both cases and controls and there were no difference in social class distribution between cases and controls on whom records were traced. A study of the North Finland Birth Cohort, which represents 93.6% of all births in Oulu and Lapland in 1966 (and covered births both at hospital and at home) also found an association between low birth weight and later schizophrenia (Jones et al, 1998).

The comparison group is smaller than the case group in this study. This rather unusual situation stems from the method of ascertainment as discussed in Sections 4.3 and 4.5.2. Briefly, controls were ascertained from the child health records where the full name and date of birth of the mother were not always listed. The availability of complete information on the mothers greatly

facilitated tracing of the birth records and therefore birth records were traced for a higher proportion of the cases than controls. In addition we were able to obtain birth records for about 200 cases on whom we had not previously obtained child health cards or school cards. This indicates that about a third of the children who were born in maternity units in Helsinki City did not subsequently attend the child health and educational systems in Helsinki city. The expansion of the suburbs around Helsinki during the 1950s and 1960s are likely to be responsible for this effect. People of all social classes moved out of Helsinki into the new suburbs of Espoo and Vantaa (*personal communication Dr Matti Huttunen*). The professional/managerial classes moved to get large houses and gardens. The manual/ labouring classes moved because of the greater availability of cheaper housing and social housing in some areas. Nevertheless the fact remains that our cases came from both migratory and non-migratory families, while the controls came from families that remained in Helsinki city from birth through to school age. However, the control group appear to be representative of the general population with regard to the frequency of various obstetric complications. A comparison of rates of complications in our controls compared with the large population-based control group from the North Finland Birth cohort (Table 4.16) shows very similar rates for individual complications, apart from pre-eclampsia.

Table 4.16 Proportions of obstetric complications in the control group compared with Finnish population figures (North Finland birth cohort 1966, Jones et al, 1998)

Pregnancy and delivery complications	Controls (n=201) (%)	1966 birth cohort (N=1,074) %
Pre-eclampsia	0.5	3.0
Diabetes	0.0	0.1
Bleeding (all trimesters)	3.5	4.5
Fever (all trimesters)	0.5	0.7
Premature (<37wks)	4.9	4.9
Fetal Presentation other than vertex	5.7	4.5
Caesarian section	4.9	4.2
Forceps delivery	0.5	1.7
Cephalo-pelvic disproportion	0.5	1.7
Birthweight<2500g	4.9	3.4

The cases and controls are not matched for year of birth or hospital of birth but the significant linear relationships between low birthweight and schizophrenia, and low ponderal index and schizophrenia persisted even after adjustment for these possible confounding factors. There was no information in the birth records on cigarette smoking or alcohol abuse during pregnancy and these possible confounders could not be adjusted for in the analysis

The Findings

A significant association between risk of later schizophrenia and both low birth weight and low ponderal index was found in this study. The mean birth weight and mean ponderal index of the cases was significantly lower than that of the controls and there was also a significant inverse linear relationship between low ponderal index and later schizophrenia, such that the lower the ponderal index the greater the risk of schizophrenia. However the differences between the groups were not large – in the region of 100g for birth weight (Table 4.14) and the groups did not differ on the category of low birth weight (<2500g) (Table 4.12). This indicates a shift in the distribution of birth weight or ponderal index in the schizophrenic group rather than a subgroup effect. Support for the distribution shift is provided by the quartile analysis.

Low birth weight has been associated with schizophrenia since the earliest days of such investigations (Rosanoff, 1934, Lane and Albee, 1966, Stabeneau and Pollin, 1968; Mednick et al, 1971, Sacker et al, 1996, Jones et al, 1998; Geddes et al, 1999). A recently-published study based on a Finnish cohort (Wahlbeck et al, 2001) reports an association between low birth weight and short length at birth and later schizophrenia. The meta-analysis of published prospective population-based studies of obstetric complications and schizophrenia reported in Chapter 2 found significant associations between two measures of low birthweight (birthweight<2000g and birthweight<2500g) and later schizophrenia.

The relationship between ponderal index and later schizophrenia has been investigated by 4 previous groups of researchers (Hultman et al, 1999; Dalman et al, 1999; Wahlbeck et al, 2001; Dalman et al, 2001). Ponderal index could not be included in the meta-analysis reported in Chapter 2 as it was reported in different ways in each study and using different cut-off points. Dalman et al, (1999) found that a PI <20 increased the risk for schizophrenia (OR 3.4, 95% C.I.

1.1-10.1), particularly in females (OR 4.1: 95% CI 1.1-15.5). Hultman and colleagues (1999) found a significant relationship between low ponderal index (less than 5th centile) and later schizophrenia in males (OR 3.1: 1.4-7.1). The other 2 studies found no relationship between low PI and schizophrenia. Possible reasons for such discrepancies between studies are discussed in detail in Chapter 2.

A low ponderal index (PI) can be the result either of premature birth or retardation of intrauterine growth. Although there was no information on exact gestational age in this study, the inverse linear relationship between low PI and schizophrenia remained significant even when those infants born prematurely (<37 weeks) were excluded from the analysis. This suggests that intrauterine growth retardation is a risk factor for schizophrenia in adulthood. The relationship between risk of schizophrenia and low ponderal index held when results were adjusted for maternal BMI.

There are few clues about why intrauterine growth retardation would have occurred. Since the mothers of the cases were anaemic during pregnancy and gave a worse impression to the midwives on admission to the delivery unit, these factors could indicate a degree of maternal malnutrition during pregnancy. The BMI of the mothers of cases in late pregnancy did not differ from the BMI of the controls (Table 4.11), but there was no information on BMI at the beginning of pregnancy. The mothers of cases gained an average 1 kg less during the course of the pregnancy than the mothers of the controls, possibly providing some evidence of maternal undernutrition.

A relationship between fetal undernutrition and adult schizophrenia is indicated by the findings that individuals who were in the first trimester in utero at the height of the Dutch famine due to the Nazi blockade in 1945 have a three-fold increased risk of subsequent schizophrenia-spectrum disorder (Susser and Lin, 1993, Susser et al, 1996). These studies on the *Dutch Hunger Winter* are discussed in Chapter 2. Wahlbeck and colleagues (2001) propose a similar mechanism for their findings of a relationship between low birth weight and short length at birth and later schizophrenia among a cohort born in Helsinki during the 1920s and 1930s. Wages were low, family sizes were high and there were food shortages in Finland at that time. However during the 1950s and 1960s there was no food shortage in Helsinki and maternal and child health care systems were very prominent.

A degree of maternal self-neglect during pregnancy is another explanation for the relationship between low ponderal index and later schizophrenia. Although food was available, the mothers of the cases may not have taken good care of themselves during pregnancy. An analysis of the British 1958 birth cohort, found that mothers of cases were significantly more likely to have a constellation of lifestyle factors during pregnancy which could affect the developing fetus (Sacker et al., 1995). They had lower weight before pregnancy, were more likely to have suffered a psychological problem and to have smoked during pregnancy, and had made fewer visits to the antenatal department. More of the births in this group were attended by untrained personnel, the parity among was greater and these mothers were more likely to have given birth to low birthweight babies. None of the mothers in this study or the study of Sacker et al (1995) were frankly psychotic during pregnancy. Dalman et al (2001) found that a higher proportion of mothers of cases received no or irregular antenatal care.

In summary, the obstetric differences found in this sample between cases and controls seem to be related to characteristics of the mother and the newborn child and development of the child in utero, rather than problems with the delivery *per se*.

4.5 Chapter summary

Background: This study was designed to investigate whether children who are diagnosed with schizophrenia in adulthood could be distinguished from their peers on school performance or on obstetric history.

Methods: The study design is a population-based case-control study nested within the birth cohort of all individuals born in Helsinki, Finland between 1951-60. Case ascertainment was from three national health care registers – 928 cases of schizophrenia were identified of whom 486 had attended school in Helsinki city. Controls were taken as the next child born in the same year listed in alphabetical order after each case in the child health clinic archives.

Elementary school records were obtained for 400 children who were diagnosed with schizophrenia in adulthood and 408 controls. Results were analysed for the four years of schooling (ages 7-11) common to all pupils. School subjects were entered into a principal components analysis and produced three factors: 'academic', 'non-academic' and 'behavioural'. These factors were compared between cases and controls after adjusting for sex and social group. Eligibility for high school, and progression to high school were investigated among cases and controls.

Obstetric records were obtained for 636 cases of schizophrenia and 203 controls. Odds ratios and 95% confidence intervals for schizophrenia in relation to individual complications were calculated and adjusted for possible confounding variables. Analysis of continuous variables in quartile groups related to the distribution in controls was carried out and tests for linear trend were applied where appropriate.

Results: With regard to school performance, cases performed significantly worse than controls only on the 'non-academic' factor, (which loaded sports and handcrafts). There were no differences between the groups on the academic or behavioural factors, and there were no significant clinical correlates of factor scores. Cases were significantly less likely than controls to progress to high school, despite similar eligibility.

With regard to obstetric complications, both low ponderal index and low birthweight were related to risk of schizophrenia in an inverse linear fashion. The mothers of the cases had lower haemoglobin during late pregnancy and gave a worse impression to the midwives on admission to the delivery unit.

Conclusion: Poor performance in sports and handcrafts in elementary school may be a risk factor for later schizophrenia, and is likely to indicate a motor coordination deficit. Lack of expected progression to high school among cases supports previous work showing deteriorating premorbid adjustment in schizophrenia. There were few differences between cases and controls on obstetric history. The differences that were found appeared to concern the characteristics of the mother and the newborn child rather than delivery complications per se. Greater understanding of the causes of intrauterine growth retardation will help us to understand more about the pathogenesis of schizophrenia.

Chapter 5

An investigation of the developmental epidemiology of schizophreniform disorder in a general population birth cohort in Dunedin, New Zealand.

5.1 Introduction

The study described in Chapter 4 found that motor-coordination deficits between ages 7 and 11 (as indicated by poor performance in sports and handcrafts) was significantly associated with risk of later schizophrenia among Finnish schoolchildren. Issues arising from this finding include: how early can such impairments be detected and whether such developmental problems are specific for schizophrenia. These issues could not be addressed easily in the Finnish cohort as the early childhood developmental records were not recorded in a standardised format until 1962 and I had only examined one outcome – schizophrenia. In order to answer these questions I carried out an analysis of a general population birth cohort in Dunedin, New Zealand. The Dunedin study has followed 1,000 children from the general population from birth to age 26 with exceptionally high follow-up rates and offers several unique advantages for investigating childhood risk factors for adult outcomes.

Firstly, a wealth of detailed childhood data, encompassing many different developmental domains, has been prospectively collected from age 3 at approximately bienniel intervals using well-established and validated instruments. As outlined in Chapter 3, different impairments have been examined in different studies using a variety of case ascertainment methods and developmental scales. As a result, conclusions about the etiological significance of developmental impairments may have been confounded by these variations. In the Dunedin cohort one can compare the effects of different types of developmental risk factors within one sample.

Secondly, one can test for specificity of early developmental risk factors for schizophreniform outcomes. Childhood developmental problems that occur in schizophrenia may occur also in patients with other psychotic and nonpsychotic disorders (Done et al, 1994; Crow et al 1995, Van Os et al, 1997; Sigurdsson et al, 1999). It is therefore unclear whether childhood developmental impairment is specific to schizophrenia or is merely a marker for a wide range of psychological disturbances in adulthood. Psychiatric diagnoses at age 26 were made on all subjects in the cohort based on structured diagnostic interviews conducted by trained health professionals thus allowing the examination of developmental risk factors for psychiatric disorders other than schizophrenia.

Thirdly, one can study whether the same developmental risk factors predict psychotic symptoms both in childhood and adulthood. An earlier report from the Dunedin cohort showed for the first time that children's self-reported psychotic symptoms at age 11 predicted a schizophreniform diagnosis at age 26 (Poulton et al, 2000). If the same (or similar) relationship can be shown between childhood developmental risk factors and age 11 psychotic symptoms as with age 26 schizophreniform disorder, then that would suggest that the psychotic symptoms at age 11 are part of the disease process itself rather than an independent risk factor.

Fourthly, information is available on birth complications and mother-child interaction thus allowing examination of the relationships between these factors and developmental factors in the development of schizophrenia.

5.1.1 Aims and Hypotheses

Aims

In this study I aimed to address the following questions.

(1) Is childhood developmental impairment across a range of domains specific to schizophrenia or does it occur in other psychotic and nonpsychotic conditions?
(2) How early can such impairments be detected?
(3) What proportion of children are affected and what is the predictive power of early developmental impairment for later schizophrenia?
(4) How do obstetric, maternal or social factors affect the association between developmental impairment and later schizophrenia?
(5) Do childhood developmental impairments predict psychotic symptoms both in childhood and adulthood?

Hypotheses

The hypotheses, informed by the previous literature review (chapter 3), were:

(1) That childhood developmental impairments would be specific to schizophrenia-related disorders,
(2) That developmental impairments could be detected from early childhood, even infancy.
(3) That the majority of children who later developed schizophreniform disorder would display some developmental impairment but that such impairments would have poor predictive power.
(4) That the presence of both developmental impairments and a history of obsetric complications would increase the risk of later schizphreniform disorder.
(5) That developmental impairment would be associated with manifestations of later psychosis across the life-span.

5.2 Study population

Participants are members of the Dunedin Study, a longitudinal investigation of health and behaviour in a complete birth cohort (Silva and Stanton, 1996). The cohort of 1037 children (52% male) was constituted at age 3 when the investigators enrolled 91% of consecutive births between April 1972 and March 1973 in Dunedin, New Zealand. Cohort families represent the full range of socio-economic status in the general population of New Zealand's South Island and are primarily white. Follow-ups have been carried out at ages 5 (n= 991), 7 (n=954), 9 (n=955), 11(n=925), 13 (n=850), 15 (n=976), 18 (n=993), 21 (n=992), and most recently at 26 years when 980 (96%) of the 1,019 Study members still alive were assessed. The basic procedure involves bringing participants to the research unit within 60 days of their birthday for a full day of individual data collection. The various research topics are presented as standardized modules, each administered by a different trained examiner. At each assessment, interview data are supplemented by questionnaires that are mailed to informants who know the subject well.

5.3 Methods and analysis

5.3.1 Childhood exposures

Socio-economic status, obstetric complications and maternal factors

Socioeconomic status. Family socio-economic status (SES) measured the average SES level of the Study members' families across the first fifteen years of life (Wright et al, 1999). A six-point scale designed for New Zealand (Elley and Irving, 1976) was used where 1=unskilled labourer and 6=professional. For analytic purposes, Study members were designated as low SES (groups 1&2) versus medium/high SES (groups 3-6).

Obstetric complications. Each child was examined shortly after birth and prenatal information was taken from the hospital records. The prevalence of these obstetric complications in the Dunedin sample is reported elsewhere (Buckfield, 1978). The obstetric complications index used in this study consisted of the sum of the following complications (Stanton et al, 1991): maternal

diabetes, glycosuria, epilepsy, hypertension, eclampsia, antepartum haemorrhage, accidental haemorrhage, placenta praevia, previous small baby, gestational age <37 weeks or >41 weeks, birth weight <2500g or >4kg; either small or large for gestational age, low Apgar score at birth, hypoxia at birth (idiopathic respiratory distress syndrome or apnoea), major or minor neurological signs, Rh incompatibility, ABO incompatibility, nonhaemolytic hyperbilirubinemia.

Definition of low Apgar score: A classification of Apgar scores was used to designate the infant as 'normal' (ie having a normal Apgar score) or as having a Type I, II or III low Apgar score as follows: Type I: At 5 minutes of life, the heart rate was less than 100 per minute, respiration irregular or absent, and the infant was centrally cyanosed. Type II: The conditions of Type I low Apgar score not fulfilled but the infant took more that 10 minutes to establish normal respiration. Type III: The conditions of Types I and II low Apgar scores not fulfilled but the infant's asphyxia at birth warranted resuscitation with an endotrachael tube and manual intermittent positive pressure respiration

Mother-child interaction: During the child's age 3 assessment, mothers were rated on their general attitude and behaviour in relation to their child, separately by the psychologist and the doctor. Mothers were rated on 8 features: harshness towards the child, critical or negative evaluation of the child, rough, awkward handling of the child, no effort to help child, unaware or unresponsive to child's needs, indifferent to child's performance, demanding of child's attention, soiled, unkempt appearance of the child (Silva, 1976). Scores from the doctor and the psychologist were summed to create a 'mother-child interaction' variable for each mother. 25% of cohort mothers received a score of 1 or more on these 8 ratings. For the purposes of this study, mothers who scored 1 or more were defined as having 'atypical mother-child interaction'.

Neuromotor development

Infant milestones were assessed retrospectively at age 3. During the assessment the mothers were asked to remember to the nearest month, when their child attained various milestones: smiling, sitting up, walking, dry-by-day, dry-by-night, fed self, talked (words) and talked (sentences). Only those responses were recorded where the mother was certain that she could recall this information accurately. Most mothers referred to their 'Plunkett books', in which cohort mothers had recorded this information as their baby developed.

Neurological abnormalities were assessed at age 3. Each child was examined by a pediatric neurologist for neurological signs, including assessment of motility, passive movements, reflexes, facial musculature, strabismus, nystagmus, foot posture and gait. This assessment was based on the procedures described by Touwen and Prechtl (1970).

Motor development was assessed at age 3 with the Bayley Motor Scales (Bayley, 1969), at age 5 using the McCarthy Motor Scales (McCarthy, 1972), and at ages 7 and 9 using the Basic Motor Ability Test (Arnheim and Sinclair, 1974).

Language and cognitive development

Receptive and expressive language development was assessed at ages 3 and 5 using the Reynell Developmental Language Scales (Reynell, 1969), which have separate subtests for receptive (verbal comprehension) and expressive language. At ages 7 and 9 years, language development was assessed using the Auditory Reception and Verbal Expression subtests of the Illinois Test of Psycholinguistic Abilities (Kirk, McCarthy and Kirk, 1968)

Intelligence was assessed at age 3 with the Peabody Picture Vocabulary Test (Dunn, 1965), at age 5 with the Stanford-Binet Intelligence Scales (Terman and Merrill, 1960), and at ages 7, 9, and 11 with the Weschler Intelligence Scales for Children-Revised (WISC-R; Weschler, 1974). All tests were administered by trained psychometrists according to standard protocol (Moffitt et al, 1993).

Emotional (internalizing) and behavioural (externalising) problems

At ages 5, 7, 9, and 11 parents and teachers completed the Rutter Child Scales (RCS; Rutter et al, 1970; Elander and Rutter 1996), a questionnaire that inquires about the major areas of a child's behavioural and emotional functioning during the past year. Parents and teachers rated each item on the RCS as: does not apply (0), applies somewhat (1), or certainly applies (2). Internalizing problems were measured by items that inquire about a child's emotional functioning and describe children who worry about many things, or who often appear miserable, unhappy and tearful. Externalizing problems were measured by items that describe children who frequently fight, bully other children, lie, steal, disobey, truant, destroy property, and have irritable tempers. The relevant items were summed across the 4 age periods and 2 raters (parents and teachers) to derive

measures indexing children's emotional (internalizing) and behavioural (externalising) problems, respectively.

Interpersonal Adjustment

Social isolation and peer rejection. At ages 5, 7, 9 and 11 parents evaluated two statements about their child: *'child is a loner'* and *'not much liked by other children'*, using a 3-point scale (as before) for each statement. At ages 7, 9 and 11 teachers independently evaluated the same statements. Mean scores were calculated separately for parents and teachers to derive two measures indexing *'social isolation'* and *'peer rejection'* respectively.

Peer attachment measures how warmly each child felt towards their peers at ages 13 and 15 years, as assessed by a self-report from the Inventory of Parent and Peer Attachment (Armsden and Greenberg, 1987). Scores ranged from 0 to 27. Mean scores for the two time periods were calculated to create a measure of peer attachment for each Study member.

Psychotic symptoms at age 11

At age 11 years study members were administered the Diagnostic Interview Schedule for Children (DISC-C) (Costello et al, 1982) by a child psychiatrist (Anderson et al, 1987). Approximately one quarter of the cohort were assessed at school and did not see the psychiatrist. The schizophrenia section of the DISC-R interview asked 5 questions regarding possible psychotic symptoms. The items were scored by the psychiatrist as 0, no; 1 yes, likely and 2, yes definitely. The scores for each item were summed. The majority of study members (86%) obtained a score of 0 (n=673), 12.5% obtained a score of 1 (n=103) and were called the 'weak symptom' group', and the 1.5% obtained a score of 2 or more (n=13) and were called the 'Strong symptom group'. Individuals in the 'strong symptom' group at age 11 were found to have a very high risk of later schizophreniform disorder at age 26 (OR 16.4, 95% CI, 3.9-67.8). Individuals in the weak symptoms group also have an increased risk of schizophreniform disorder at age 26 (OR 5.1, 95% CI, 1.7-18.3) but to a lesser degree (Poulton et al, 2000)

5.3.2 Adult psychiatric outcomes

At age 26, symptoms were ascertained using the Diagnostic Interview Schedule (DIS) (Robins et al, 1995) administered by health professionals with either a medical or masters degree at minimum. Psychiatric interviews at age 26 were complete for 976 of the 1,019 cohort members still living. The reporting period was 12 months prior to interview. The Axis I disorders diagnosed at age 26 were grouped into the following diagnostic outcome groups (following groupings found in DSM-IV): (a) schizophreniform disorder (3.7%), (b) manic episodes (2.0%), (c) depressive disorders (15.7%), comprising major depressive episode and dysthymia; (d) anxiety disorder (23.7%) comprising generalized anxiety disorder, panic disorder, agoraphobia, social phobia, obsessive-compulsive disorder, post-traumatic stress disorder, and specific phobia. In order to create a comparison group of non-psychotic disorders groups, (c) and (d) were then combined and termed the anxiety/depression group (28.5%). The primary outcome for this study was schizophreniform disorder. For the purposes of this analysis, subjects who were co-morbid for two or more disorders were assigned to one diagnostic group only, in the following order of priority: schizophreniform disorder, mania, anxiety/depression.

Procedures for ascertaining schizophreniform cases are explained in detail by Poulton et al (2000). High rates of psychotic symptoms (but not necessarily schizophrenia) have been found in general population based surveys (McGorry et al, 1995, Verdoux et al 1998, Van Os, 2000, Poulton et al, 2000) indicating that such symptoms may be more common in the general population than previously suspected. Moreover the DSM-IV Criterion A for schizophrenia can be fulfilled relatively easily with two symptom types and may lead to inappropriate case ascertainment and over-diagnosis of schizophrenia in epidemiological samples (Kessler et al, 1994, Kendler et al, 1996). Therefore, several changes were made to the DSM-IV diagnostic criteria (APA, 1994) to enhance diagnostic validity as follows: an age-26 diagnosis of schizophreniform disorder used in this study required (1) hallucinations and (2) at least two other symptoms from Criterion A of DSM-IV, plus (3) evidence of impairment in social or occupational functioning. Hallucinations and delusions were ascertained via self-report, disorganised speech via observer ratings, and social and occupational impairment via informants' reports as well as self-report. Thirty-six Study members (3.7%) met these criteria. Symptoms were present in all cases for at least one month (required for a schizophreniform disorder

diagnosis), and were continuously present in 9 cases (1% of cohort) for 6 months or longer (required for a schizophrenia diagnosis).

5.3.3 Statistical Analysis

The age-26 psychiatric outcomes were coded into four mutually exclusive diagnostic groups, representing the schizophreniform, mania, anxiety/depression, and control groups, respectively. Chi-square tests were used to examine the relation between sex (0 = female; 1 = male), family SES (0 = low; 1 = medium/high), and adult psychiatric disorders. Because there were significant differences between diagnostic groups and both sex and SES, these two variables were subsequently entered as covariates in all analyses.

The raw scores for childhood developmental variables were first standardized on the entire cohort using the z-score transformation, so that the cohort had a mean = 0 and a standard deviation = 1 on these variables. Fgures 5.1 –5.4 show the standardised scores for the developmental variables in each outcome group at different age points. The relations between childhood developmental impairments and age-26 psychiatric outcomes were examined using a collection of regression techniques, as required for each of the different types of developmental variables examined in this study (categorical, continuous, and repeated). Each regression equation comprised 3 dummy variables for diagnostic status (representing the schizophreniform, mania, and anxiety/depression groups, respectively), with the control group as the reference category. Sex and SES were entered as covariates in all regression analyses.

Logistic regression analysis was used to analyze the following categorical variables: presence of one or more neurological signs at age 3, maternal rejection, and individual obstetric complications. Adjusted odds ratios (AOR) and their 95% confidence intervals (C.I are reported. Ordinary least squares regression was used to analyze the following interpersonal variables: peer rejection and social isolation. Data on motor and language development, IQ, and internalizing and externalizing problems were available as repeated measures over at least 4 occasions for Study members. As discussed in Chapter 1, the analysis of repeated measures from longitudinal studies is complicated by the opportunity for missing data (Diggle, Liang and Zeger, 1994, Everitt, 1998). Even with the high follow-up rates in the Dunedin Study, missing data for

different subjects at each of the assessment ages creates a situation where power may be compromised when using listwise deletion across multiple measurement occasions. New techniques for analysing longitudinal data such as the generalised estimating equation (GEE) approach (Liang and Zeger,1986) that is used in the present study, are specifically formulated so that they can accommodate non-informative missing values in the models used. GEE is a form of repeated measures regression analysis in which any required covariance structure may be assumed and parameters estimated without specifying the joint distribution of the repeated observations. The parameters represent the average difference between subjects. In the present study, we used GEE as implemented in Stata version 6.0 (Statacorp, 1999, Rabe-Hesketh and Everitt, 2000), specifying an unstructured correlation matrix and using robust standard errors to protect against model misspecification. Standardized regression coefficients, adjusted for sex and SES, and their 95% confidence intervals are reported.

To test whether the relations between developmental impairments and age-26 psychiatric outcomes obtained independently of both perinatal and postnatal environmental factors, all aforementioned regressions were repeated after also including scores on the obstetric complications scale and the maternal rejection scale respectively as additional covariates in separate models. To test whether the childhood developmental impairments that were associated with the age-26 schizophreniform diagnosis were also associated with age-11 psychotic symptoms, the regression analyses were repeated using two dummy variables to represent the 'weak' and 'strong' psychotic symptom groups at age 11, with the non-symptom group as the reference category. For these analyses, regression coefficients, adjusted for sex and SES, and their 95% confidence intervals were reported. All analyses were carried out using Stata version 6.0 (StataCorp, 1999). All significance tests were two-tailed.

Power calculations

Previous cohort studies (Jones et al, 1994; Jones and Done, 1997) have found a difference of between 0.3 and 0.5 standard deviations in childhood cognitive test scores between cases of schizophrenia and general population controls. This study had 83% power at 95% significance (two-tailed test) to detect a difference of 0.5 standard deviations in developmental scores between cases (n=36) and controls (n=642), 64% power to detect a difference of 0.4 standard deviations, and 54% power to detect a difference of 0.3 standard deviations.

5.4 Results

Sex and socio-economic status and psychiatric outcomes

There were significant overall sex and SES differences between diagnostic groups (Table 5.1). Post hoc analyses showed that the schizophreniform group had significantly lower SES than controls (χ^2 = 16.5 (df=1), p<0.01), and the anxiety/depression group contained significantly more females than the control group (χ^2 =17.6 (df=1), p<0.01).

Table 5.1 The relation between Study members' diagnostic status at age 26 and their sex and social class origins

DSM-IV diagnoses at age 26		**Sex N (%)**		**Socioeconomic Status N (%)**	
Diagnostic groups	*N (%)*	*Male*	*Female*	*Low*	*Medium/High*
Control	642 (65.8)	353 (55)	289 (45)	123 (19.2)	519 (80.8)
Schizophreniform	36 (3.7)	21 (58.3)	15 (41.7)	17 (47.2)	19 (52.8)
Mania	20 (2.0)	12 (60)	8 (40)	3 (15.0)	17 (85.0)
Anxiety/Depression	278 (28.5)	111 (39.9)	167 (60.1)	57 (20.5)	221 (79.5)
Chi-square (df)		19.1 (3), p < 0.01		16.8 (3), p < 0.01	

Obstetric complications, atypical mother-child interaction and psychiatric outcomes

Obstetric complications- overall score

There was a significant association between the overall obstetric complication index and later schizophreniform disorder, (Adjusted regression coefficient = 0.39, 95% CI, 0.05-0.72, p = 0.02), but no significant association with later mania or anxiety/depression groups.

Individual obstetric complications

Analysis of the separate obstetric complications (Table 5.2) revealed that 3 obstetric complications were associated with an increased risk of schizophreniform disorder: low Apgar score at birth (Odds ratio adjusted for sex and SES (AOR) = 5.9, (95% CI: 1.1-32); hypoxia at birth (apnea or idiopathic respiratory distress syndrome), (AOR = 5.0 (95% CI: 1.5-16.4); and small-for-gestational-age status (AOR = 2.8 , (95% CI: 1.1-6.9).

Mother-child interaction

Mothers of the schizophreniform group were significantly more likely to be rated as having 'atypical mother-child interaction' when compared with mothers of the control group (42.5% vs 19.4%, AOR 2.6 (95% CI:1.2-5.6), p=0.01). There was no significant association between atypical mother-child interaction and later mania or anxiety/depression.

Table 5.2 Obstetric complications in relation to risk of later schizophreniform disorder, mania and anxiety/depression

Obstetric complication	Controls (n=642)	Schizophreniform disorder (n=36)		Mania (n=20)		Anxiety/Depression (n=278)	
	No. exp.	No. exp.	OR (95% ci)	No. exp	OR (95% ci)	No. exp.	OR(95% ci)
Para 1	192	14	1.6 (0.8-3.1)	8	1.6 (0.6-3.8)	102	1.3 (0.99-1.8)*
Para 4+	131	4	0.4 (0.1-1.2)	5	1.3 (0.5-3.7)	56	1.0 (0.7-1.4)
Maternal diabetes	7	0	-	0	-	1	0.4 (0.04-3.2)
Maternal hypertension	55	4	1.2 (0.4-3.7)	0	-	24	0.9 (0.6-1.6)
Antepartum haemorrhage	10	1	1.6 (0.2-13.0)	1	3.6 (0.4-29.5)	4	0.8 (0.3-2.7)
Forceps delivery	133	7	1.0 (0.4-2.4)	6	1.6 (0.6-4.2)	59	1.1 (0.8-1.6)
Caesarian section	29	2	1.6 (0.4-7.3)	0	-	14	1.02 (0.5-1.9)
Apgar <10	6	2	5.9 (1.1-32.0)*	0	-	3	1.1 (0.3-4.8)
Hypoxia (apnoea/IRDS)	16	4	5.0 (1.5-16.4) **	0	-	14	1.9 (0.9-3.9)
Small for gestational age	48	7	2.8 (0.01-6.9)*	2	1.4 (0.3-6.2)	25	1.2 (0.7-1.9)
Premature (<37 wks)	27	0	-	0	-	10	0.8 (0.4-1.8)
Rhesus/ABO/ jaundice	9	0	-	1	3.7 (0.4-31.7)	4	1.1 (0.6-5.5)
Neurological signs at birth	15	3	2.8 (0.7-10.6)	1	2.2 (0.3-18.2)	8	1.3 (0.5-3.1)
Low birth weight (<2500g)	32	2	1.12 (0.2-4.9)	1	1.0 (0.1-7.7)	9	0.6 (0.3-1.3)
Length (<48cm)	26	2	1.4 (0.3-6.1)	0	-	11	0.9 (0.4-1.8)
Head circ.<31cm	4	0	-	0	-	4	2.03 (0.5-8.2)

IRDS = idiopathic respiratory distress syndrome; * p<0.05; ** p<0.01

Neuromotor development and psychiatric outcomes

Infant milestones and neurological abnormalities. The schizophreniform group began to walk significantly later than controls, (mean schizophreniform group = 14.9 months (95% CI:12.9-16.9) vs mean control group = 13.6 months (95% ci 13.4-13.9), t = 2.2 (df=663), p = 0.02), but there were no differences between the groups on any other infant milestones. At age 3, the schizophreniform group were significantly more likely than controls to have one or more neurological signs, as assessed by a pediatric neurologist (AOR =4.6, 95% CI: 1.9-10.9). The manic group (AOR = 0.8, 95% CI :0.1-6.4) and the anxiety/depression group (AOR = 1.7, 95% CI: 0.9-2.8) were not significantly more likely to have neurological signs than controls.

Motor development. The schizophreniform disorder group performed worse than controls (more than 0.3 sd) on standard tests of motor skill at ages 3, 5 and 9, but not at age 7 (Figure 5.1). The repeated measures analysis adjusting for sex and SES effects, showed that the schizophreniform group performed significantly worse than the control group overall, while the mania group performed significantly better than the controls (Table 5.2). The anxiety/depression group did not differ significantly from controls on any of these motor assessments

Cognitive and language development and psychiatric outcome

The schizophreniform group performed more poorly than controls (about 0.4 sd) on standard IQ tests at each of 5 assessments between ages 3 and 11 (Figure 5.2). The schizophreniform group did not exhibit any problems with expressive language (Figure 5.3), but their receptive language skills were significantly poorer than those of the controls (between 0.2 and 0.6 sd) between ages 3 and 9 (Figure 5.4). These impairments among the schizophreniform group were independent of sex and SES (Table 5.2). The mania or the anxiety/depression groups did not differ significantly from controls on either language measure or on IQ test performance

Fig.5.1 Mean standardised scores for motor development at ages 3, 5, 7 and 9

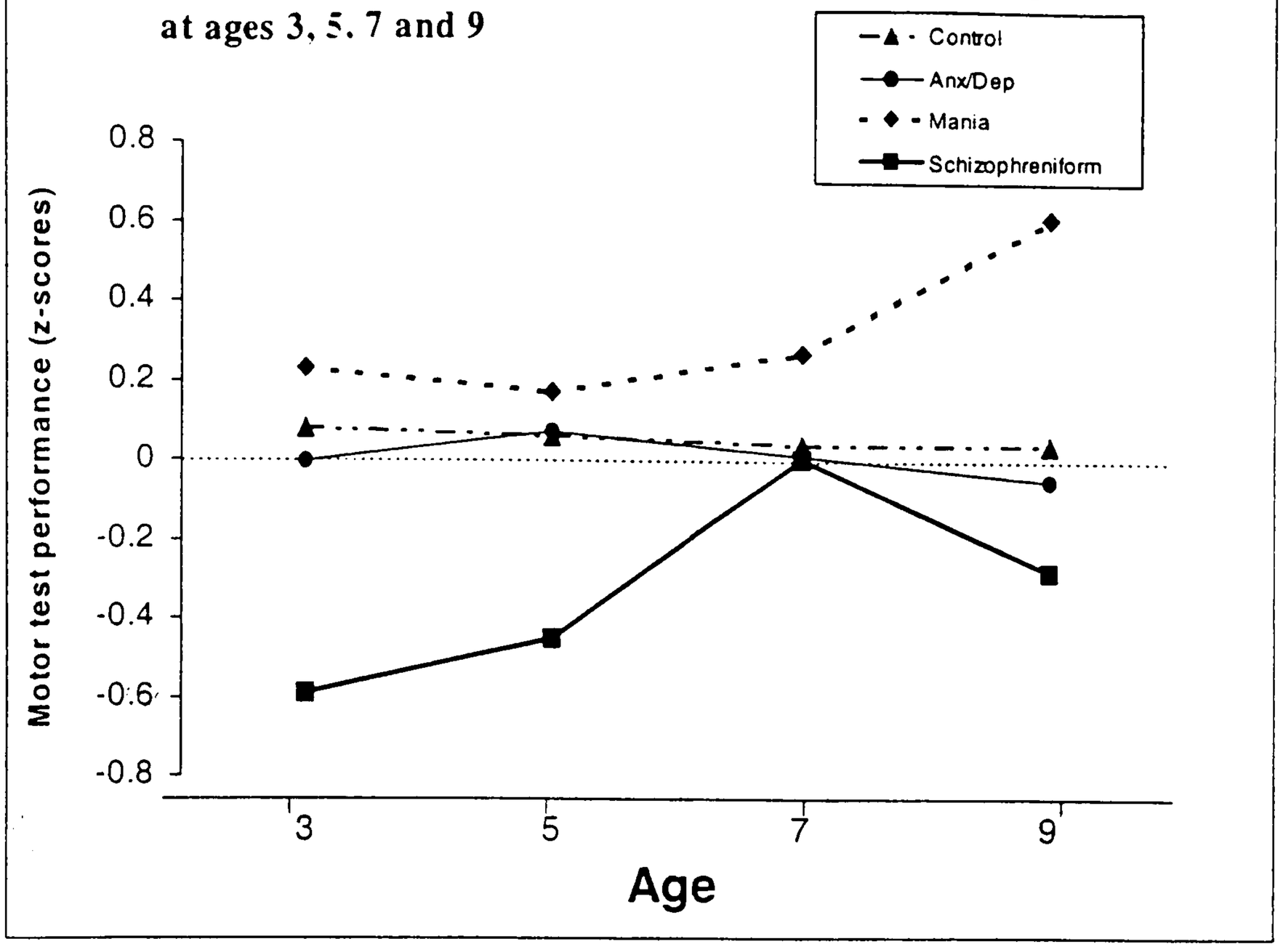


Fig 5.2 Mean standardised full-scale IQ at ages 3, 5, 7, 9, 11

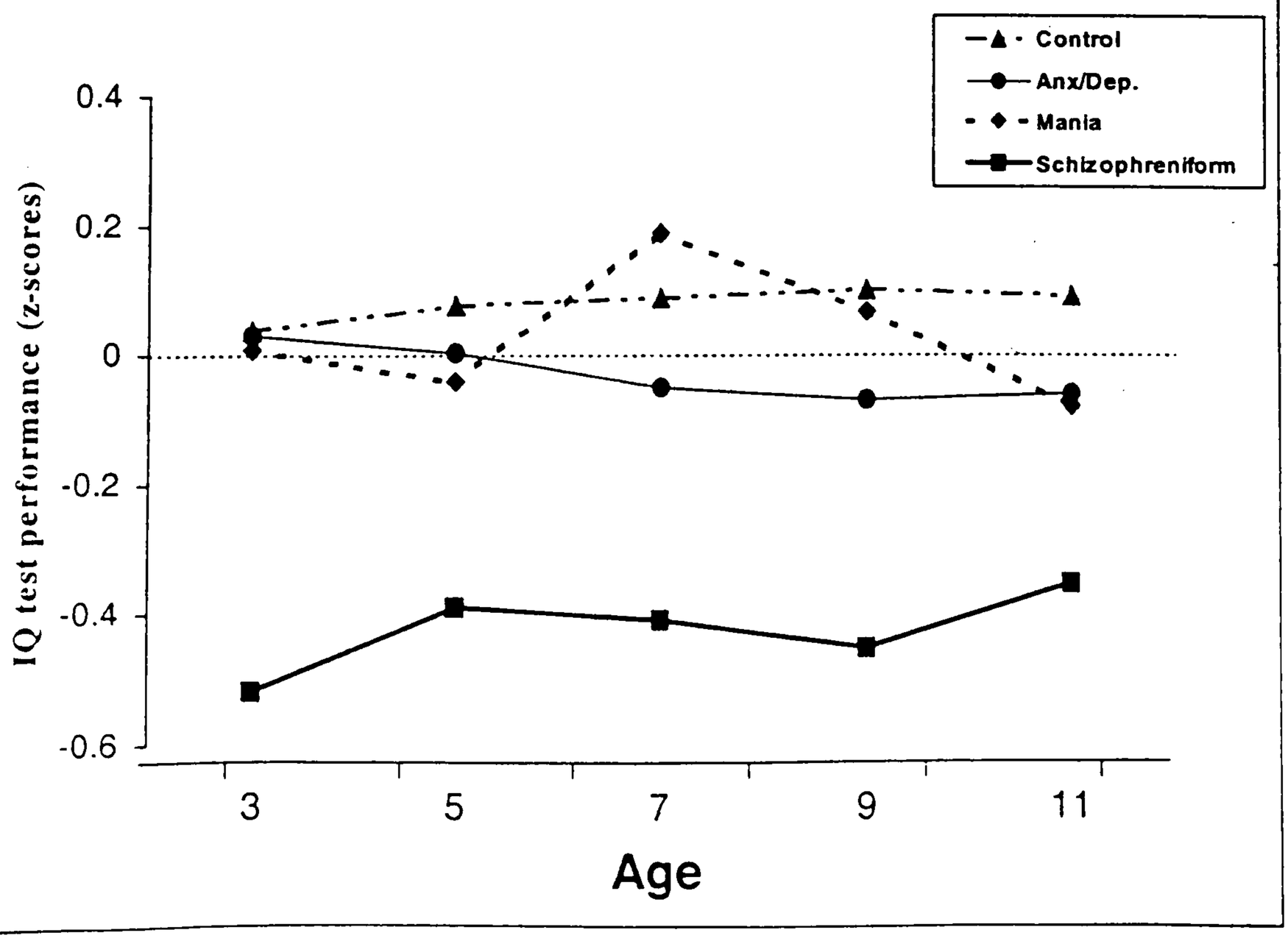


Fig 5.3 Mean standardised expressive language scores at ages 3, 5, 7 and 9

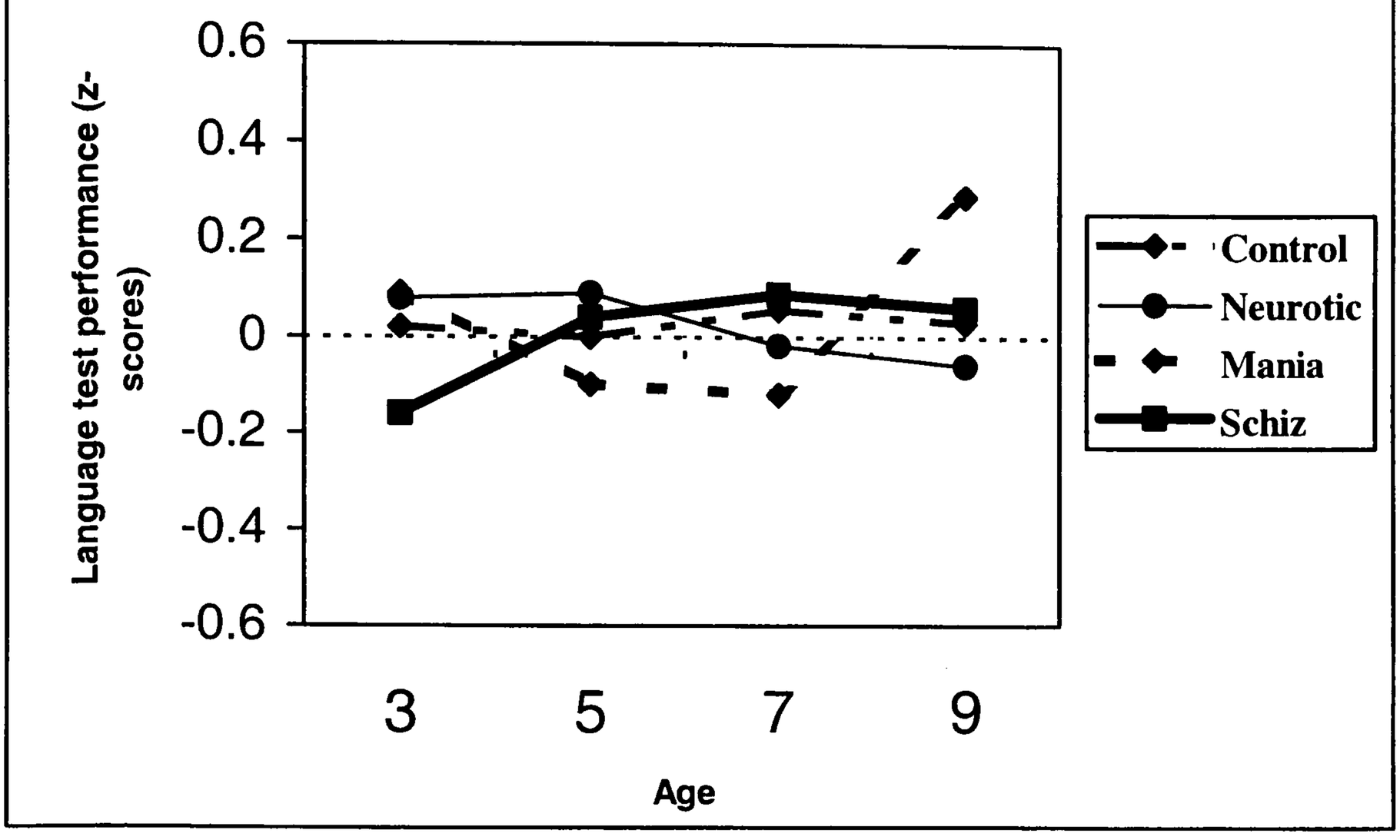
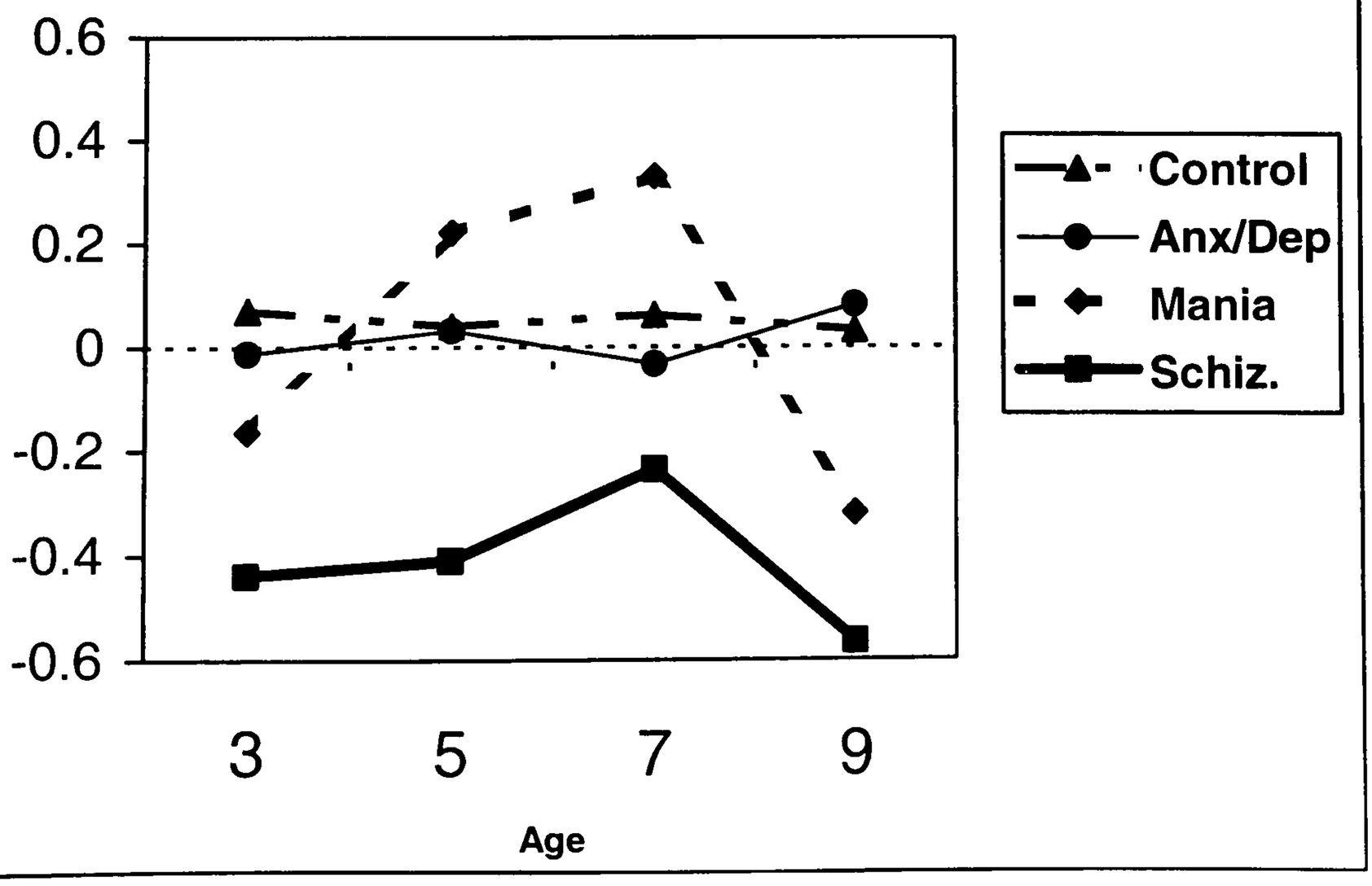


Figure 5.4. Mean standardised receptive language scores at ages 3,5,7 and 9



Emotional, behavioural and interpersonal problems and psychiatric outcomes

The anxiety/depression group scored significantly more highly than controls on parent-rated internalizing problems and, less significantly, on parent-rated antisocial behaviours (Table 5.4). Cohort members who fulfil criteria for schizophreniform disorders at age 26 scored significantly more highly than controls on teacher-rated internalizing problems and teacher-rated antisocial behaviours (Table 5.4). Study members who fulfil criteria for mania at age 26 do not differ significantly from the remainder of the cohort on any of these measures, though a trend for an excess of parent-rated antisocial behaviour may have achieved significance with larger numbers in the group. Study members who fulfil criteria for neurotic disorders at age 26 scored significantly more highly than controls on parent-rated, (but not teacher-rated) social isolation, (Table 5.5). The other two diagnostic groups did not differ from controls on either measure of social isolation. Teacher- rated peer rejection was higher in all three diagnostic groups compared with controls and this effect was most significant for schizophreniform disorder (Table 5.5). Parent-rated peer rejection was higher for mania and neurotic disorder (but not for the schizophreniform disorder) compared with controls.

Combined parent-teacher ratings: On the combined parent/teacher rating, the schizophreniform group and particularly the anxiety/depression group exhibited significantly more childhood internalizing problems than controls (Table 5.6). These effects were independent of sex and SES. The schizophreniform and mania groups exhibited more childhood externalizing problems than the control group (Table 5.6). The mania group and the anxiety/depression group, but not the schizophreniform group, were significantly more likely to experience childhood social isolation.
All three diagnostic groups were significantly more likely than the control group to be rejected by peers as rated by parents and teachers (Table 5.6). The mania group and the anxiety/depression group, but not the schizophreniform group, were significantly more likely to experience childhood social isolation.

Poor peer attachment: Study members who fulfil criteria for schizophreniform disorders at age 26 reported themselves as significantly lower than controls on the peer attachment rating (Table 5.7). The neurotic disorder group also scored significantly worse on this measure, though to a lesser degree.

Table 5.3 Motor and language development (ages 3, 5,7 and 9) and IQ (ages 3,5,7,9,11 and 13) in schizophreniform disorder, mania and neurotic disorders, (lower scores indicate worse performance)

	Motor Development				Expressive Language				Receptive Language				IQ			
	Coeff.	*SE*	*z-test*	*p*	*Coeff.*	*SE*	*z-test*	*p*	*Coeff.*	*SE*	*z-test*	*p*	*Coeff.*	*SE*	*z-test*	*p*
Schiz*	-0.39	0.12	-3.3	0.001	0.09	0.12	0.84	0.4	-0.31	0.12	-2.5	0.01	-0.33	0.13	-2.5	0.01
Mania*	0.33	0.16	2.1	0.04	0.11	0.15	0.69	0.5	0.02	0.16	0.14	0.9	0.12	0.17	0.67	0.5
Neurotic*	-0.05	0.05	-1.1	0.3	-0.03	0.05	0.24	0.6	-0.04	0.05	-0.8	0.4	-0.07	0.05	-1.39	0.2
Covariates																
Sex**	-0.04	0.04	-1.1	0.28	-0.18	0.04	-4.4	<0.0001	-0.08	0.04	-1.9	0.06	-0.01	0.05	-0.29	0.77
SEG #	0.17	0.05	3.19	0.001	0.36	0.05	6.9	<0.0001	0.52	0.05	9.3	<0.0001	0.61	0.06	10.05	<0.0001

*Baseline group are controls; ** baseline group is female, # baseline group is low social class

Table 5.4 Psychological and behavioural development: parent and teacher-rated psychological symptoms (ages 5,7, 9, and 11) in schizophreniform, mania and neurotic disorders. (Higher scores indicate higher levels of symptoms)

	Internalizing problems Parent rating				**Internalizing problems Teacher rating**				**Antisocial behaviour Parent rating**				**Antisocial behaviour Teacher rating**			
	Coeff.	*SE*	*z*	*p*	*Coeff.*	*SE*	*z*	*P*	*Coeff.*	*SE*	*z*	*p*	*Coeff.*	*SE*	*z*	*p*
Schiz*	0.34	0.25	1.4	0.17	0.4	0.19	2.1	0.03	0.46	0.27	1.7	0.08	0.6	0.24	2.6	0.01
Mania*	0.45	0.32	1.4	0.2	0.39	0.25	1.6	0.1	0.61	0.35	1.7	0.08	0.5	0.31	1.6	0.1
Neurotic*	0.35	0.1	3.4	0.001	0.09	0.08	1.2	0.2	0.23	0.11	2.1	0.04	0.07	0.09	0.7	0.5
Covariates																
Sex**	-0.18	0.092	-1.9	0.05	0.02	0.07	0.31	0.7	0.42	0.1	4.2	<0.0001	0.51	0.09	5.8	<0.0001
SEG #	-0.21	0.09	-2.5	0.01	-0.221	0.09	6.21	0.01	-0.6	0.12	-4.8	<0.0001	-0.56	0.11	-5.2	<0.0001

*Baseline group are controls; ** baseline group is female, # baseline group is low social class

Table 5.5 Childhood social / interpersonal adjustment: social isolation and peer rejection rated by parents and teachers (higher scores indicate worse adjustment) and self-reported peer attachment (lower scores indicate poorer attachment).

	Social Isolation Parent rating (mean score 5-11 years)				Social Isolation Teacher rating (mean score 7-11 years)				Peer Rejection Parent rating (mean score 5-11 years)				Peer Rejection Teacher rating (mean score 7-11 years)			
	Coeff.	*SE*	*t*	*p*	*Coeff.*	*SE*	*t*	*p*	*Coeff.*	*SE*	*t*	*p*	*Coeff.*	*SE*	*t*	*p*
Schiz*	0.04	0.17	0.21	0.8	0.22	0.17	1.3	0.2	0.19	0.17	1.1	0.3	0.49	0.17	2.8	0.005
Mania*	0.36	0.22	1.62	0.1	0.36	0.22	1.6	0.1	0.51	0.22	2.3	0.02	0.38	0.22	1.7	0.08
Neurotic*	0.19	0.07	2.7	0.006	0.05	0.07	0.6	0.5	0.16	0.07	2.2	0.03	0.14	0.07	1.9	0.05
Covariates																
Sex**	0.12	0.06	1.9	0.06	0.07	0.06	1.1	0.3	0.01	0.06	0.17	0.8	0.04	0.06	0.56	0.57
SEG #	-0.22	0.07	-2.7	0.007	-0.17	0.08	-2.2	0.03	-0.27	0.08	-3.4	0.001	-0.31	0.08	-3.8	<0.001

*Baseline group are controls; ** baseline group is female, # baseline group is low social class

Table 5.6 Combined parent and teacher ratings of emotional, behavioural and interpersonal adjustment in subjects who later fulfil diagnostic criteria for schizophreniform disorder, mania and neurotic disorder, (higher scores indicate worse adjustment).

	Internalizing behaviours (5-11 years)				Antisocial behaviour (5-11 years)				Social Isolation (mean score 5-11 years)				Peer Rejection (mean score 5-11 years)			
	Coeff	SE	Z test	p	Coeff	SE	Z test	p	Coeff	SE	t	p	Coeff	SE	t	p
Schizophreniform	0.27	0.13	2.1	0.03	0.32	0.14	2.3	0.02	0.17	0.18	0.9	0.3	0.46	0.23	2.0	0.045
Mania*	0.28	0.17	1.6	0.09	0.36	0.18	1.9	0.048	0.46	0.18	2.4	0.01	0.54	0.26	2.0	0.042
Neurotic*	0.17	0.05	3.1	0.002	0.09	0.06	1.7	0.09	0.16	0.07	2.1	0.04	0.16	0.08	2.1	0.03
Covariates																
Sex**	-0.07	0.04	-1.4	0.17	0.31	0.05	6.1	<0.001	0.12	0.06	1.8	0.06	0.04	0.06	0.6	0.55
SEG #	-0.12	0.06	-2.1	0.04	-0.4	0.06	-6.1	<0.001	-0.25	0.07	-3.4	0.001	-0.34	0.09	-3.8	<0.001

*Baseline group are controls; ** baseline group is female, # baseline group is low social class

Table 5.7 Mean self-reported peer attachment at ages 13 and 15 year and later psychiatric outcomes

Outcome	Peer attachment Self report (mean score 13 & 15 years)			
	Coeff.	*SE*	*t*	*p*
Schizophreniform	-0.5	0.16	-2.9	0.003
Manic	-0.2	0.21	-0.9	0.34
Neurotic	-0.1	0.06	-2.5	0.012
Covariates				
Sex	-0.8	0.06	-14.0	<0.0001
SEG	0.2	0.05	4.7	<0.0001

Relationship between obstetric complications, maternal factors and developmental deviance among the schizophreniform group

In view of the association between certain obstetric complications and maternal rejection and later schizophreniform disorder, I investigated whether the relations between developmental deficits and schizophreniform disorder were independent of these perinatal and postnatal factors. After adjusting for the obstetric complications that were significantly related to schizophreniform outcome and sex and SES, the associations between schizophreniform disorder and motor development (Coeff. = -0.37 (95% CI: –0.61, -0.14), p=0.002), receptive language development (Coeff. = -0.25 (95% CI: –0.49, -0.015) p=0.037), and cognitive development (Coeff. = -0.29 (95% CI: –0.55, -0.04), p= 0.025), all remained significant. Similarly, after adjustment for maternal rejection and sex and SES, the associations between schizophreniform disorder and motor development (Coeff. = -0.37 (95% CI: –0.61, -0.13), p=0.002), receptive language development (Coeff. = -0.27 (95% CI: –0.5, -0.03), p=0.03), and cognitive development (Coeff. = –0.31 (95% CI: –0.056, -0.05), p=0.02), all remained significant. The relationship between developmental deviance and later schizophreniform disorder remained significant after adjusting for obstetric complications and maternal rejection in the same model. There was no significant interaction between obstetric complications and developmental impairment in increasing the risk for schizophrenia in adulthood.

Relationship between childhood developmental impairment and self-reported psychotic symptoms at age 11

Self-reported 'strong' psychotic symptoms at age 11 were associated with significant developmental impairments in the domains of neuromotor, receptive language, cognitive and emotional development (Table 5.8). The effect sizes were generally even larger than those noted for schizophreniform disorder at age 26. Weak psychotic symptoms at age 11 were generally not significantly associated with childhood developmental impairments. However the direction of the coefficients were generally in the same direction as the 'strong' symptom group.

Table 5.8 Childhood developmental impairments in children who reported psychotic symptoms at age 11

	Weak Symptoms (Score=1) (N=103)		**Strong symptoms (score>1)(N=13)**	
Dependent variables	*Coeff.* (95% CI)*	*p*	*Coeff.* (95% CI)*	*p*
Motor development	-0.11 (-0.25, -0.02)	0.1	-0.62 (-1.2, -0.04)	0.03
Expressive language	0.015 (-0.11, 0.14)	0.8	-0.11 (-0.42, 0.19)	0.5
Receptive language	-0.14 (-0.27, -0.005)	0.04	-0.57 (-0.92, -0.22)	<0.01
IQ	-0.12 (-0.26, 0.03)	0.1	-0.52 (-0.83, -0.21)	<0.01
Internalizing problems	0.15 (-0.05, 0.34)	0.1	0.74 (0.18, 1.3)	0.01
Externalizing problems	0.15 (-0.03, 0.33)	0.1	0.34 (-0.28, 0.94)	0.28
Peer rejection	0.17 (-0.03, 0.37)	0.1	0.51 (-0.2, 1.2)	0.16
Social isolation	0.03 (-0.17, 0.24)	0.7	0.46 (-0.14, 1.06)	0.14

*Baseline group are children who did not report psychotic symptoms at age 11 (n=673). All coefficients are adjusted for sex and SES.

Risk of severe early developmental impairment in relation to risk of later psychiatric disorder.

I examined the risk of being in the lowest tertile for all three developmental domains (motor, receptive language and cognition) ie an indicator of severe early developmental impairment, within the 3 psychiatric outcome groups compared with controls (Table 5.9). Only the schizophreniform group were significantly more likely than controls to exhibit severe early developmental impairment: 26.5 % compared with 7.5% of controls.

Table 5.9 The risk of being in the lowest tertile for 3 developmental measures (motor, receptive language and IQ) at age 3 in relation to risk of later psychiatric disorder.

Diagnosis		Number of subjects in the lowest tertile for all 3 measures	Risk of being in the lowest tertile	
	Total N	*N (%)*	*OR (95% ci)**	*p*
Control	573	55 (9.6%)	1	
Schizophreniform	32	9 (28.1%)	2.8 (1.2-6.5)	0.02
Mania	18	2 (11.1%)	0.5 (0.1-4.2)	0.56
Neurosis	251	26 (10.4%)	1.1 (0.7-1.8)	0.65

* adjusted for sex and social class

Distribution of developmental impairment among the schizophreniform group within developmental domains

The schizophreniform group were consistently overrepresented (53-56%) in the lowest tertiles (thirds) of the population distribution for motor, language or cognitive development at age 3 (Table 5.10). The summary odds ratios for risk of schizophreniform disorder across tertiles for each of these three developmental measures at age 3 indicated significant linear trends in risk for schizophreniform disorder with increasing developmental impairment within each domain, ie a dose-reponse relationship within each domain.

Table 5.10 Percentage of schizophreniform disorder group in each tertile and analysis of linear trends: motor, language and cognitive development at age 3

Developmental domain at age 3	Distribution of developmental scores (33.3% of controls in each tertile)			Test for linear trend	
	Highest Tertile %	*Middle tertile %*	*Lowest Tertile %*	*OR (95% ci)*	*p-value*
Motor					
% schizophreniform. group	28	16	56	1.6 (1.03-2.6)	0.01
Receptive language					
% schizophreniform. group	25	22	53	1.6 (1.03-2.6)	0.01
IQ					
% schizophreniform group	16	31	53	2.6 (1.3-5.3)	0.03

Distribution of developmental impairment among the schizophreniform disorder group across developmental domains

I also examined risk for schizophreniform disorder with increasing degrees of developmental impairment across developmental domains (Table 5.11). Twenty-eight percent of the schizophreniform group were in the lowest tertile for all three developmental domains (motor/language/cognitive) at age 3, compared with 9.5% of controls (OR 6.0 (0.9-19.1). A test for linear trend was again significant, indicating a dose-response relationship between developmental impairment and later schizophreniform disorder across developmental domains. Only 16% of the schizophreniform group were not in the lowest tertile at age 3 for any of the three developmental domains assessed.

Table 5.11 Risk of schizophreniform disorder according to degree of developmental impairment at age 3 (indexed by being in the lowest tertile for 0, 1, 2 or 3 developmental domains).

No of developmental domains severely affected (motor/language/IQ)	Controls N=571 (%)	Schizophreniform disorder N=32 (%)	OR (95% ci) adjusted for sex and social group
0	243 (42.5)	5 (16)	Baseline
1	166 (29)	10 (31)	2.9 (0.99-9.01)
2	108 (19)	8 (25)	3.03 (0.96-9.6)
3	54 (9.5)	9 (28)	6.02 (0.9-19.1)
Test for linear trend: OR (95% ci)			1.8 (1.3-2.6)
			Z = 3.6; p<0.001

Predictive value of developmental deficits in childhood for schizophreniform disorder

I examined whether being in the lowest tertile for all three developmental domains (motor, receptive language and cognitive) at age 3 had any predictive value for schizophreniform disorder. The sensitivity of this developmental model was 26.5% (9/31 cases of schizophreniform disorder detected), and the specificity (the proportion of true negatives correctly detected) was 92.5%. The positive predictive value of this 'developmental' model was 16.6% (9/63 subjects), with a false positive rate of 85% (54/63 subjects). Addition of information on obstetric complications, (low APGAR score, hypoxia-related complication or SGA), and maternal rejection to the developmental model resulted in a positive predictive value of 66% (4/6 subjects) but the sensitivity of this 'enhanced' model was only 13% (4/31 cases detected).

Table 5.12 Childhood developmental variables, obstetric variables and maternal variables at age 3 as predictors of schizophreniform disorder at age 26.

Risk group	Sensitivity % (n)		Specificity % (n)		Positive Predictive Value % (n)		False Positive Rate % (n)	
Developmental risk only	29.0	(9/31)	90.5	(517/571)	14.3	(9/63)	85.1	(54/63)
OC risk only	29.0	(9/31)	90.2	(513/569)	13.8	(9/65)	86.2	(56/65)
Maternal risk only	41.9	(13/31)	80.5	(460/571)	10.5	(13/24)	89.5	(111/124)
Developmental + OC	16.1	(5/31)	98.8	(562/588)	41.7	(5/12)	58.3	(7/12)
Developmental +maternal	19.3	(6/31)	95.7	(555/580)	27.3	(6/22)	72.7	(16/22)
Developmental + OC + maternal	12.9	(4/31)	95.5	(567/594)	66.7	(4/6)	33.3	(2/6)

5.5 Discussion

Methodological issues

Although the Dunedin Study has many advantages for studying childhood risk factors for adult outcomes, as outlined in the introduction, some limitations should be mentioned.

Firstly, the sample sizes in the psychotic groups are not large. However, power calculations showed that there would be sufficient power (83%) to detect a difference of 0.5 standard deviations between cases of schizophreniform disorder and controls – an effect size detected in previous cohort studies (Jones and Done, 1997). It might seem that a large number of tests were carried out on a relatively small number of cases of schizophreniform disorder. However the purpose of this investigation was to examine many domains of development within the same sample – something that most other studies have not been able to do. I wanted to examine whether there was a 'pan-developmental' deficit in schizophrenia – a notion that was suggested by the previous literature reviewed in Chapter 3 (and eventually borne out by the results). Although this strategy increased the possibility of Type II errors, the significant developmental impairments in the schizophreniform group were consistently detected on bienniel testings over 8 years, and were independent of sex and social class effects.

A second possible problem is that the Study members are still in their twenties and have not passed through the entire period of risk for psychosis. Although, strictly speaking, one is dealing with early-onset cases only in this study, similar childhood developmental risk factors for schizophrenia have been described in a cohort study that has followed subjects up to age 43 years (Jones et al, 1994) suggesting that these findings can be extrapolated throughout the age-incidence distribution. Lastly, throughout this analysis I have reported on findings for schizophreniform disorder rather than schizophrenia alone, mainly because of sample size considerations, but also because dimensional or continuum models of psychosis are becoming established as the most likely theoretically (Claridge et al, 1994) and the most useful clinically (van Os et al, 1999). In support of this it is notable that the childhood developmental risk factors for schizophrenia found in other cohorts (Jones et al, 1994, Crow et al. 1995) (see Chapter 3) are so similar to the developmental risk factors for the broader phenotype of schizophreniform disorder in this cohort.

5.5.2 The findings

This longitudinal investigation of an unselected birth cohort examined a number of childhood developmental exposures in relation to three adult psychiatric outcomes. Children who later fulfilled diagnostic criteria for schizophreniform disorder at age 26 exhibited significant impairments in a range of developmental domains (neuromotor, language, cognitive, emotional, and interpersonal development) from as early as 3 years of age. In contrast, children who later fulfilled diagnostic criteria for mania and anxiety/depression exhibited problems only in the areas of emotional and interpersonal development. Early neuromotor, language, and cognitive developmental impairment therefore appear to show specificity to schizophreniform disorder, whereas childhood emotional and interpersonal difficulties are associated with a range of psychiatric disorders in adulthood. The finding that similar childhood developmental deficits were noted for both self-reported psychotic symptoms at age 11 and later schizophreniform disorder at age 26 suggests that these early childhood developmental risk factors are associated with psychotic illness processes that begin in childhood.

There was no evidence that the association between early childhood developmental impairment and later schizophreniform disorder was a subgroup effect. Only one sixth of the schizophreniform group were not in the lowest tertile at age 3 for at least one of the three developmental domains assessed. This indicates the ubiquity of developmental impairment among these children from at least preschool years onward. The risk of later schizophreniform disorder increased in a linear fashion with degree of early motor, language and cognitive impairment both within and across these developmental domains. Although from a public health point of view the predictive power of early developmental impairment in this cohort was not great, about 16%, interventions to improve early childhood development are likely to have many positive benefits above and beyond any preventive effect on schizophrenia.

The relationship between neuromotor developmental problems and later schizophreniform disorder in this study was particularly strong, with evidence of delay in learning to walk during infancy, an excess of neurological signs at age 3, and significant impairments on repeated motor testing between ages 3 and 9. The schizophreniform group exhibited deficits in receptive language development (verbal comprehension) rather than expressive language development. Previous work on this cohort has shown that receptive but not expressive language delay at 3 years was significantly associated with behaviour problems in later childhood (Silva et al, 1987)

and a follow-up study of a group of children who suffered from developmental receptive language disorder in childhood found that 10% later developed schizophrenia (Howlin et al, 2000). This analysis shows that childhood cognitive impairments among the schizophreniform group were early-emerging and persistent, with significant deficits in IQ detectable even from age 3. The findings from this study on motor, language and cognitive impairments are remarkably consistent with other cohort studies showing childhood developmental deficits among individuals with schizophrenia (Jones et al 1994, Crow et al 1995, Cannon et al, 1999). For example, the age at first walking for the cases in this study is 1.3 months on average later than controls and in the 1946 British birth cohort the delay was 1.2 months (Jones et al, 1994).

These results differ somewhat from studies that have shown childhood developmental disturbances among other psychiatrically disordered groups. Two studies have noted childhood motor and speech defects among individuals with affective disturbance and affective psychosis, but these abnormalities were mainly confined to childhood or adolescent onset cases (van Os et al, 1997, Sigurdsson et al, 1997). In addition the developmental data reported in Sigurdsson et al (1999) were based on psychiatric casenote information rather than on objective developmental measures. Crow et al (1995) found low educational test scores impairments among children from the 1958 birth cohort who were destined to develop psychiatric illness in adulthood: preschizophrenic children performed worst, followed by preneurotic children and pre-affective psychosis children were least impaired. One difference from this cohort is that the neurotic subjects were diagnosed on the basis of hospital admission data, and are thus probably not representative of the majority of individuals with neurotic disorder.

One area of debate is the etiology of developmental precursors for schizophrenia. A genetic etiology is suggested by the occurrence of developmental problems in 25-40% of children at genetic high risk for schizophrenia (see Chapter 3) (Fish, 1992, Marcus et al, 1993; Hans et al, 1999), but it has also been postulated that maternal and social variables, (Sobel, 1961, Ragins et al, 1975, Goodman, 1987, Yoshida et al, 1999) or obstetric factors (Rieder et al, 1977, Fish, 1992, Marcus et al, 1993) may be partly responsible for these effects. A comprehensive view of development that takes into account both perinatal (Pasamanick et al, 1956) and post natal (Sameroff and Chandler, 1975) environmental factors will best allow us to reach an understanding of the developmental processes involved in the genesis of psychopathology (Cicchetti and Cannon, 1999).

The availability of perinatal and maternal data in this cohort allowed analysis of the effects of these factors on early developmental risk factors for schizophrenia. As discussed in chapter 2,

there is evidence that obstetric complications involving fetal/ neonatal oxygen deprivation and fetal growth retardation are significantly related to the risk of later developing schizophreniform disorder (Dalman 1999, Jones et al, 1997, Cannon et al, 2000b, Rosso et al, 2000b, Zornberg et al, 2000). Such effects were noted in this study. However, in agreement with a series of investigations from the National Collaborative Perinatal Project (Cannon et al, 2000a, Rosso et al, 2000a, Bearden et al, 2000), I found that these obstetric complications do not entirely account for the early motor, language and cognitive impairments found in the schizophreniform group. Also there was no interaction between obsetric complications and developmental impairment in increasing the risk for later schizophrenia. Analyses from other birth cohort studies (Jones et al, 1994, Myhrman et al, 1996) have shown that poor mothering, and unwantedness of a child are associated with an increased risk of later schizophrenia. There was a significant association between maternal rejection and later schizophreniform disorder, but maternal rejection does not significantly contribute to the motor, language and cognitive developmental impairments noted in the schizophreniform group. One can therefore surmise that these early developmental impairments most likely reflect the expression of schizophrenia susceptibility genes rather than the influence of perinatal or postnatal environmental factors. Reports of developmental impairments among offspring at high genetic risk for schizophrenia provide support for this view (Fish et al, 1992, Marcus et al, 1993, Erlenmeyer-Kimling et al, 2000, Hans et al, 2000).

Emotional problems and poor interpersonal functioning in childhood were associated with a host of different adult psychiatric outcomes at age 26, including schizophreniform disorder, manic episodes, and anxiety/depression disorders. These predictive associations are of actuarial interest – they span more than 15 years and do not exhibit specificity to any one outcome. Lack of specificity is important because it indicates a common pathway to the development of a range of different disorders. Although this constellation of childhood behaviours observed as early as 5 years of age is unlikely to represent a 'prodrome', it is possible that it indexes, more generally, a vulnerable personality that is at risk for all adult psychiatric disorders.

Neuroticism, antisocial behaviour and social isolation in childhood, as rated by parents, (but not by teachers), were significantly associated with adult neurotic disorder. On the other hand, teachers reported more peer rejection, antisocial behaviour and neuroticism among children who later developed schizophreniform disorder – none of which were noted by the parents. One can speculate that teachers more accurately detect precursors of later schizophrenia while parents more accurately detect precursors of later neurotic disorders (Olin and Mednick, 1996). Teacher ratings of peer rejection were higher for all three psychiatric disorder groups compared with controls, indicating that childhood peer rejection is a relatively non-specific marker for adult

psychopathology. One unexpected finding from this study was the lack of association between ratings of childhood social isolation and later schizophrenia. However many previous studies reporting schizoid tendencies as precursors to schizophrenia, have used child guidance clinic samples which are by nature selected for childhood psychopathology, (Rutter, 1984, Jones et al, 1994, Cannon M et al, 2001). Interestingly though, self-report ratings by Study members show a highly significant association between poor peer attachment in adolescence and later schizophreniform disorder. This fits with reports on sample of conscripts showing that poor social functioning is the most significant predictor of later schizophrenia in late adolescence, (Malmberg et al, 1998, Davidson et al, 1999). It is possible that pre-existing peer problems become more evident during adolescence or that difficulties for pre-schizophreniform children emerge at that time.

In conclusion, this study has demonstrated that schizophreniform disorder is associated with childhood developmental deficits in a range of domains and that these developmental deficits are early-emerging, persistent and specific to schizophreniform disorder. In addition this is the only study to demonstrate that this pan-developmental impairment is associated with psychotic symptoms both in childhood and adulthood. Taken as a whole, the evidence from this study supprts the notion that schizophrenia is '*a multisystems disorder with a longitudinal phenotype*' (Jones, 1997).

5.1 Chapter Summary

Background: This study reports an investigation of early childhood developmental risk factors for later psychiatric disorder in a one-year birth cohort (1972-73) of 1037 children - the Dunedin Multidisciplinary Health and Development Study.

Methods: The cohort was assessed at bienniel intervals between ages 3 and 11 years on a range of developmental domains, including emotional, behavioural and interpersonal problems, motor and language development, and intelligence. At age 11 children were asked about psychotic symptoms. At age 26, psychiatric status was ascertained using the Diagnostic Interview Schedule and DSM-IV diagnoses were made. Study members having schizophreniform disorder (n=36; 3.7%) were compared to healthy controls and also to groups diagnosed with mania (n=20; 2%), and non-psychotic anxiety or depression disorders (n=278; 28.5%).

Results: Emotional problems and interpersonal difficulties were noted in children who later fulfilled diagnostic criteria at age 26 for any of the psychiatric outcomes assessed. However, significant childhood impairments in neuromotor, receptive language, and cognitive development were additionally present only among the children later diagnosed with schizophreniform disorder. Early developmental impairments also predicted self-reported psychotic symptoms at age 11. The relations between developmental impairment and schizophreniform disorder were independent of the effects of sex, socio-economic status, and obstetric or maternal factors. Risk of schizophreniform disorder was increased in a linear fashion with degree of early developmental impairment both within and across domains of development.

Conclusion: These results provide evidence for an early-emerging, persistent, pan-developmental impairment that is specifically associated with schizophreniform disorder, and shows that childhood developmental impairments predict psychotic symptoms both in childhood and adulthood.

Chapter 6

Conclusions

6.1 What has been learnt from this thesis?

Novel methodological aspects of the research reported in this thesis have included the use of a nested case-control study design and the application of techniques such as multilevel modelling and the generalised estimating equation approach to the study of the developmental epidemiology of schizophrenia. The results of the studies reported in this thesis have advanced our knowledge of the developmental epidemiology of schizophrenia in a number of ways as outlined below.

A longitudinal perspective

This thesis traces the developmental profile or trajectory between birth and adolesence of children destined to develop schizophrenia in adulthood. The more detailed developmental data from the Dunedin Study is complemented by the greater statistical power of the Finnish Study. The specialised developmental tests carried out by trained personnel in Dunedin complement the standard school teacher reports in Finland. The availability of information both from the 'laboratory' and the 'real world' allows one to see how relatively subtle developmental deficits translate into everyday functioning.

This thesis establishes that developmental risk factors precede adult schizophrenia in a large population-based study in Finland. The effects were not large but were significant due to the high power of the study. The deficits found in sports and handcrafts among schoolchildren who later developed schizophrenia most likely indicate motor-coordination impairment. The Dunedin Study supports this interpretation and shows that motor developmental deficits can be detected from age 3 through to at least age 9 using standardised repeated tests of motor development. There are clues that motor problems occur even earlier, as evidenced by delayed age at first walking.

The Dunedin Study also showed consistent cognitive and language developmental impairments on repeated standardised assessments between ages 3 and 9. Once again these effects are small (about third to one half of a standard deviation below the controls) but significant. However the Finnish study, shows that, under the right teaching circumstances and social environment, that such developmental impairments do not necessarily lead to poor school performance.

However by adolescence the ability of these vulnerable children to overcome their developmental handicaps is beginning to wane. Despite achieving the necessary grades at age 11 to progress to the academic high school system in Finland, the children who were destined to develop schizophrenia are more likely to remain on in the elementary school and finish their education there. It is likely that social and interpersonal adjustment difficulties are proving a significant hurdle. In the Dunedin Study we see evidence of problems with peer attachment on self-report at ages 13 and 15 among the children who later fulfil criteria for schizophreniform disorder, whereas earlier they did not seem to have obvious difficulties with social adjustment (at least none that could be detected by parents or teachers). These difficulties may have emerged with the unique social pressures and difficulties of adolescence.

A continuum perspective

The adult schizophrenia outcome examined in the Finnish study is principally a narrowly-defined register-based diagnosis. In contrast, the outcome of schizophreniform disorder used in the Dunedin Study is a broader diagnosis – a type of 'schizophrenia-in-waiting' and not all of these subjects will go on to get an adult diagnosis of schizophrenia. Nevertheless it is intriguing that the same developmental risk factors appear to apply to both groups. Indeed, the same developmental risk factors even predict psychotic symptoms at age 11 indicating that the processes of developmental impairment and incipient psychosis are intimately intertwined from a very early age.

Specificity

The Dunedin study demonstrates that early-emerging motor, language and cognitive developmental deficits are specific to schizophrenia-spectrum psychiatric outcomes and do not occur in association with other psychotic conditions (such as mania) or non-psychotic psychiatric disorders (such as anxiety and depression). This shows that early developmental impairment is not just a non-specific risk factor for a range of psychiatric pathology in adulthood but provides a

valuable clue to the processes affected in schizophrenia-related illnesses. It is interesting that the emotional and behavioural problems that were originally associated with schizophrenia (Kraepelin, 1896, Bleuler 1908, 1911) are not, in fact, specific to the condition and indicate risk for a broad range of psychological and psychiatric disorders in adulthood. This reduces their value as predictors for schizophrenia but could be useful from the public health perspective in devising interventions for early detection or even prevention of common disorders such as anxiety and depression.

What is the role of obstetric complications?

The meta-analysis reported in Chapter 2 shows that complications of pregnancy (bleeding, diabetes and rhesus variables), complications of delivery (particularly asphyxia) and problems with fetal growth and development are all significantly associated with (small) increases in the risk for later schizophrenia. Three obstetric complications were associated with later schizophreniform disorder in the Dunedin study: low apgar score at birth, hypoxia at birth and small-for-gestational age. These complications fit within the categories identified as important by the meta-analysis. The Finnish study adds to the literature by finding an inverse linear relationship between both low ponderal index and low birth weight and later schizophrenia. The fact that these relationships persist even when premature infants are excluded shows that intrauterine fetal growth retardation is the most likely reason for this relationship.

Relationship between obstetric and developmental risk factors

Both the Finnish study and the Dunedin Study allow examination of the possible relationship between obstetric and developmental risk factors for schizophrenia within the same individuals. In this thesis the relationship between developmental impairment and later schizophrenia remained significant after controlling for the presence of obstetric complications in both studies. This indicates that obstetric complications are mediating their effect on risk of schizophrenia through a different mechanism. The data on maternal rejection from the Dunedin Study additionally allowed examination of the association between poor mothering, developmental impairment and schizophrenia. Controlling for maternal rejection did not affect the association between developmental impairment and later schizophrenia, although again there was not sufficient power to examine for interactive effects. In any case it appears that neither obstetric complications nor maternal factors can entirely 'explain' the relationship between childhood developmental impairment and later schizophrenia.

The nature of the relationship between childhood developmental impairment and later schizophrenia

This thesis shows that developmental impairment affects the majority of individuals with schizophrenia not just a 'developmental subgroup'. In the Dunedin study only 16% of individuals who later fulfilled diagnostic criteria for schizophreniform disorder were not in the lowest tertile for at least one developmental domain at age 3. The more developmental impairment that was present, (either within domains or across domains of development) the higher the risk of schizophreniform disorder. The Finnish study showed that developmental problems, as indexed by poor performance in motor-co-ordination skills were not related to age at onset of the illness, chronicity or degree of genetic vulnerability. In other words there were no particular subgroups of patients, such as those with a positive family history or early age at onset who were particularly more likely to have developmental problems. Equally, a history of developmental problems does not appear to have implications for the course or outcome of the condition.

6.2 Future developments in developmental epidemiology

The developmental epidemiology of schizophrenia points to early causes of this syndrome. It might, one day, underpin an agenda for prediction and primary prevention – before any overt signs of psychosis have emerged. Knowledge of the developmental precursors to schizophrenia may suggest the timing and content of preventive interventions. This is not yet feasible because, as demonstrated in Chapter 5, the predictive power of any models in current cohort studies is low due to the combination of modest relative risks, involving fairly common characteristics and a relatively rare outcome. It is a much safer proposition to identify who will not get the disorder, than those who will.

As discussed in Chapter 1 development is not a straightforward process. Each individual develops at his or her own rate within certain broad parameters. The study of developmental epidemiology is complicated by the fact that the researcher is studying the development of a disorder as well as the development of an individual. These separate but interacting trajectories make teasing apart the two processes more difficult. Development involves chains or trajectories not single risk factors. There are usually many mediating factors to be considered, both known and unknown. We need to study causal processes rather than individual risk factors.

All along we will need to be aware of the impressive plasticity of the brain during development. The genes while they set the program do not by any means determine the outcome. Once a child suffers a developmental perturbation in any domain, then its micro- or social environment is changed and the development of brain and mind will also be affected. This might further impinge upon the environment, setting-up what has been termed a 'self-perpetuating cascade of abnormal development' (Jones, et al., 1994). The limitations of currently-available statistical methods and study designs do not allow us easily to test such 'cascade' models. Psychiatric illnesses are the result of complex gene-environment and gene-gene interactions and exhibit a great deal of heterogeneity. We need to find out about protective factors and resilience as well as risk factors. We need to understand how certain events at critical periods can alter the course of development. Our biology is not our destiny and vulnerabilities, if identified and understood, need not turn into psychiatric disorders.

New conceptual approaches in epidemiology entail broadening the notion of causation in two directions. Firstly, risk factors have traditionally been modelled as static characteristics of the individual, whereas disease causation is a dynamic process that involves a time dimension and an interplay of causal interactions (Kreiger, 1994). As demonstrated in this thesis, introducing the element of development over time is necessary and causation should be considered in terms of a pathway over a life course rather than in terms of a certain set of risk factors at a set point in time.

Secondly, many writers have bemoaned the obsessive preoccupation of epidemiology with individual-level risk factors (Susser M, 1998; Tauber, 1995). Epidemiology needs to embrace many levels of investigation, preferably within the same framework: the individual level, the microlevel (molecular level) and the societal level, and also a time dimension to enable the study of dynamic processes (Susser and Susser, 1996; Schwartz, 1999). This means that in an investigation of schizophrenia we may need to consider characteristics of the society, such as level of development, characteristics of individuals, including development over time , and genetic and molecular factors. Not only does the environment vary over time but genes are expressed at varying times and to varying extents. Statistical and epidemiological methods that can encompass dynamic and multi-level processes will need to be developed and refined, (Susser E et al, 2000).

Further investigation of developmental markers in schizophrenia will require extremely large samples that incorporate genetic information and will pose a major challenge for traditional cohort designs. Whether necessary samples and investigations can be funded will be a matter for society as much as for scientists (Jones, 1999). Collaboration and cross fertilisation will be needed

between researchers in other disciplines, particularly neuroimaging, genetics, statistics, molecular and developmental biology, and also with other chronic disease epidemiologists investigating the early origins of adult health, for instance in the area of cardiovascular disease or diabetes, (Leon and Ben-Schlomo, 1999, McKeigue, 1999). The same cohorts and methods can often be useful to researchers in different fields. It is increasingly evident that mental and physical health are linked in many ways throughout life, and research on early adult exposures should consider outcomes in both domains (Susser E et al 1999). There is no point reinventing the wheel for each disorder. Luckily this sharing process has already begun with the extension of David Barker's work (Barker, 1992) into the field of schizophrenia (Wahlbeck et al, 2001).

We now have the chance to enter a 'new age of epidemiology for schizophrenia' (Susser E et al, 2000). The combination of new paradigms and larger cohorts, with the tools of modern epidemiology and biomedical science has the potential to greatly advance our understanding of the causal pathways to schizophrenia. This will not be an endeavour for epidemiology alone. It is increasingly evident that understanding the complex molecular mechanisms underlying brain growth, connectivity and maturation will be crucial to understanding the etiology of schizophrenia.

6.3 Epilogue

Completion of this thesis does not conclude the lines of investigation described here. Numerous challenges lie ahead but the key to further progress requires a continued emphasis on the concept of development. The Human Genome Project will allow us to pose and answer questions about the role of particular genes in brain development, although the possibility of gene therapy or modification remains a distant dream. In the meantime we can continue our search for potentially modifiable environmental risk factors that convert vulnerability into illness. The journey to prevent schizophrenia or understand the causes of the disorder is likely to take us even further back into childhood - even to prenatal life.

"*And so we beat on, boats against the current, drawn back ceaselessly into the past.*"

(F. Scott Fitzgerald, *The Great Gatsby*)

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